REMARKS

By the present amendments, claims 12, 21, and 22 have been amended. Claims 1-11 were previously cancelled without prejudice and, thus, claims 12-22 are currently under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, in the Office Action dated November 3, 2009, claims 12-22 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 12-20 of co-pending U.S. Application No. 11/406,296. Although Applicants acknowledge this rejection, Applicants respectfully request that the rejection be held in abeyance until the claims of the pending application or the conflicting claims of U.S. Application No. 11/406,296 are indicated as being allowable. At such a time, Applicants will then address the Examiner's double patenting rejection.

In the Office Action, the Examiner then rejected claims 12-22 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,488,041 ("Barbier") in view of U.S. Patent No. 3,637,641 ("Huber"). In particular, the Examiner took the position that a person of ordinary skill in the art would have found it obvious to administer a bisphosphonic acid derivative to treat lameness caused by osteoarthritis in a horse because Barbier teaches that bisphosphonic acid derivatives are useful for treating bone disorders and Huber teaches that bony exostosis is a common bone disorder characterized by lameness and difficulty in locomotion or limping. However, both Barbier and Huber

teach away from the present invention because they are directed to treatments targeting bone and not osteoarthritis-induced lameness wherein the target is cartilage, and thus the combination of Barbier and Huber do not make the claimed invention obvious. Accordingly, for the reasons set forth in more detail below, Applicants submit that this rejection is respectfully traversed and should be withdrawn.

Contrary to the Examiner's assertions, one of ordinary skill in the art would not have found it obvious, in light of the teachings of Barbier and Huber, to utilize bisphosphonic acid derivatives for treating lameness caused by osteoarthritis as this specific aspect of the claimed treatment is not taught or suggested in either Barbier or Huber. Instead, these references relate directly to treatments involving bone and not to osteoarthritis-induced lameness which directs the treatment to cartilage tissue and not bone, which, again, is the target of the treatment in both Barbier and Huber. As such, Barbier actually **teaches away** from the present claims, and there is no reason for a person of ordinary skill in the art to utilize the bisphosphonic acid derivatives described in Barbier as being useful for the bone fracture treatment, in the treatment of lameness caused by osteoarthritis which is focused on cartilage tissue.

Moreover, in the Office Action, the Examiner stated that Barbier broadly teaches that bisphosphonic acid derivatives are useful in treating bone disorders when this is not the case. In fact, Barbier does **not** teach or suggest that bisphosphonic acid derivatives are useful for "any bone disorder", but instead is specifically directed to a method of promoting bone repair and specifically indicates that its methods are to be used following a bone fracture or bone surgery to promote bone repair. See, e.g., col. 3 lines 13-14; see

also col. 2, lines 59-63. As such, and once again, the treatment of an osteoarthritis-related condition would not be suggested by treatments to bone injury of the type described by Barbier.

In addition, there is nothing in the Huber reference which when added to Barbier would direct one skilled in the art towards the present claims. Huber is directed toward the use of the protein orgotein to treat bony exostosis and, more specifically, the use of orgotein to **lessen** the bone formation that occurs with bony exostosis (see, e.g., col. 8, lines 17-27, which discusses the arresting of osteophyte development subsequent to orgotein administration). As such, one of ordinary skill in the art would not have even been led in the first place to combine the bisphosphonic acid derivatives of Barbier, which are described as **promoting** bone growth, with the teachings of Huber as doing so would effectively destroy the lessening of bone formation that is indicated as desirable in Huber. Additionally, one of ordinary skill in the art would certainly not have combined Barbier with Huber for the treatment of lameness cause by osteoarthritis, as both of those references are directed to treating conditions where the primary therapeutic target is bone, instead of the cartilage that is the primary therapeutic in lameness caused by osteoarthritis, as described in further detail below.

In the Office Action, however, the Examiner asserted that the recitation of "lameness caused by osteoarthritis" in the claims of the present application carried little patentable weight because lameness would still be clinically the same regardless of the etiology or origin of the disorder causing the lameness. In the first place, to the extent that the Examiner took the position that such language was not positively stated in the

previous claims, the present amendments now make it clear that this element is a positive aspect of the claims. Even further, Applicants submit that lameness caused by osteoarthritis differs significantly from other lameness disorders and is a distinct condition with a distinct origin.

Indeed, lameness can arise from many varying disorders including osteoarthritis, rheumatoid arthritis, and various injuries, including penetrating wounds of the foot, gravel, bruising, and corns (see the attached reference by DeBouces, et al., Veterinary Clinics of North America: Equine Practice, 5(1): 179-194, 1969). For example, lameness caused by rheumatoid arthritis arises as a result of an inflammatory disease, with inflammation of the synovium being the primary consequence of the disorder (see, e.g., the attached reference by Bonney, et al., Script Report: Innovation in arthritis treatment: A market revolution at pages 31-32). Lameness may also be caused by bone injuries such as fractures.

However, lameness caused by osteoarthritis, on the other hand, is a distinct condition that develops from a non-inflammatory degenerative joint disease that is characterized by a splitting and fragmentation of the articular cartilage and further differs from lameness caused by rheumatoid arthritis in that it primarily results from a degeneration of the joint tissue, as also described on pages 31-32 of the attached Bonney, et al. reference. As such, it is generally recognized in the field that lameness caused by osteoarthritis is a distinct condition from lameness caused by other reasons, such as rheumatoid arthritis or bone fractures, and, indeed, one of ordinary skill in the art would recognize that treatments for a distinct type of lameness, e.g., those associated with bone

injuries wherein the target is bone, or rheumatoid arthritis where the target is the synovial membrane (as described further below), may be the opposite of treatments for ailments such as osteoarthritis-induced lameness wherein the target is cartilage.

In this regard, it is also noted that the medical management of osteoarthritis-induced lameness is further distinct from both the treatment of lameness caused by injuries and the treatment of lameness caused by rheumatoid arthritis. As reflected in the attached reference entitled Diagnosis and Management of Lameness in the Horse, osteoarthritis-induced lameness requires a specific medical management that is focused on the symptomatic relief of the disorder and on arresting the progression of joint degeneration (page 746). Indeed, as cartilage loss is commonly regarded as the hallmark of osteoarthritis-induced lameness, the medical treatments typically include non-steroidal anti-inflammatory drugs, corticosteroids, hyaluronan, polysulfated glycosaminoglycan, pentosan polysulfate, glucosamine, and chondroitin sulphate (see pages 746-751).

It is thus again the case that one of ordinary skill in the art would not have any reason to select a bisphosphonic acid derivative from Barbier and make use of it in a method of treating osteoarthritis-induced lameness, as described and claimed in the present application. Rather, one of ordinary skill in the art would have necessarily been led away from the use of a bisphosphonic acid derivative and would have been led to select a drug such as glucosamine or chondroitin sulphate as these drugs were already known to those of ordinary skill in the art as being particularly useful for treating osteoarthritis-induced lameness and its underlying conditions.

Accordingly, the Barbier reference which is directed to treatment targeted to bone **teaches away** from the present claims, and one skilled in the art would **not** have expected that the methods described in Barbier, which are directed to the use of bisphosphonic acid derivatives following bone fractures or bone surgeries, would be used to treat any form of lameness, much less one that targets a completely different tissue, namely cartilage tissue such as in the present invention.

As indicated in the Annex attached hereto, the methods of the present application, which make use of bisphosphonic acid derivatives for the treatment of osteoarthritis-induced lameness, are designed to be practiced on horses whose lameness is marked by osteoarthritis and cartilage loss and thus, unlike the methods in Barbier, is specifically targeted to cartilage tissue. The attached Annex provides data from a recent *in vivo* study by the Applicants of the present application, wherein it has been found that tiludronic acid (i.e., 4-chlorophenylthiomethylenebisphosphonic acid, is capable of reducing the progression of osteoarthritic cartilage lesions and promoting proper cartilage healing. Such results are neither taught nor suggested in Barbier or Huber as, again, these two references are directed to bone disorders and thus teach away from treatment targeting cartilage. Neither the Barbier or Huber reference provide any teaching or suggestion that bisphosphonic acid derivatives should be used for the treatment of osteoarthritis-induced lameness, and indeed because these references relate to treatments to bone injuries, these references teach away from the present claims.

In short, there is simply no teaching or suggestion in either Barbier or Huber, alone or in combination, that would have led one of ordinary skill in the art to utilize a

bisphosphonic acid derivative for the treatment of osteoarthritis-induced lameness, and instead these references teach away from the present claims because they are directed at most to treatment of bone fractures or other bone injuries and do not target cartilage tissue as in the present case wherein the treatment of osteoarthritis-induced lameness is involved. As described above, osteoarthritis-induced lameness is a distinct condition that has a distinct origin and is thus commonly treated in a manner that is distinct from other lameness disorders, particularly those arising from bone-related injuries.

Accordingly, Applicants submit that neither the Barbier and Huber references, either alone or in combination, anticipate or make obvious Applicants' claimed invention, and the Examiner's rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicant submits that the present application overcomes all prior rejections and objections and has been placed in condition for allowance. Such action is respectfully requested.

Respectfully submitted,

Date: May 3, 2010

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ANNEX 1

Investigation over a one-year period of the effect of treatment with a bisphosphonate, tiludronic acid (TA), on the development of osteoarthritic (OA) cartilage lesions in dogs, which after anterior cruciate ligament (ACL) transection were subjected to reconstructive surgery.

Methods: ACL transection was performed on dogs on DO and extracapsular stabilization (ECS) on D28. Dogs were randomly divided into two groups: 15 received placebo and 16 were treated with TA (2 mg/kg) via subcutaneous injection on D14, D28, D56 and D84. Magnetic resonance images were acquired on D-10, D26, D91, D210 and D357, and cartilage volume quantified. At sacrifice (D364), cartilage from femoral condyles and tibial plateaus was macroscopically and histologically evaluated. Expression levels of MMP-1, -3, -13, ADAMTS-4, -5, BMP-2, FGF-2, IGF-1, TGF-β-I, collagen type II and aggrecan were determined using real-time RT-PCR.

Results: The loss of cartilage volume observed after ACL transection was stabilized following ECS. Thereafter there was a gradual gain in cartilage volume with a significant reduction in cartilage loss on the tibial plateaus at D91 ($p<0.02$) and D210 ($p<0.001$) in the TA-treated dogs. At sacrifice (D364), TA-treated dogs presented significant reduction compared to placebo in the severity of macroscopic ($p=0.03$ for plateaus) and histological ($p=0.07$ for plateaus) cartilage lesions, had a better preserved collagen network as well as decrease in MMP-13 ($p=0.04$), MMP1 and MMP-3 expression levels.

Conclusion: Treatment with TA reduces progression of OA cartilage lesions in dogs that suffer an acute ACL injury followed by ECS surgery. TA efficacy is mediated by a reduction in the synthesis of the catabolic factor MMP-13, which exerts a protective effect on the collagen network.

18. Stashak TS: Lameness. *In* Stashak TS (ed): Adams' Lameness in Horses. Edition 4. Philadelphia, Lea & Febiger, 1987, p 551
19. Trotter GW, McIlwraith CW, Norrdin RW, et al: Degenerative joint disease with osteochondrosis of the proximal interphalangeal joint in young horses. J Am Vet Med Assoc 180:1312, 1982
20. Turner AS, Gabel AA: Lag screw fixation of avulsion fractures of the second phalanx in the horse. J Am Vet Med Assoc 167:306, 1975
21. Yovich JV, Stashak TS, Sullins KE: Bilateral hind limb pastern arthrodesis in a horse. Equine Vet J 18:79, 1986

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Penetrating Wounds, Abscesses, Gravel, and Bruising of the Equine Foot

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The horse's hoof is a seemingly tough, durable, and renewing structure, but it is in nearly constant contact with the external environment. As such, a wide variety of traumatic insults may damage the hoof and the enclosed structures. Penetrating injuries, with or without development of infection, and concussive injury causing bruising are common causes of lameness. In this article we review these categories of foot injuries causing lameness.

PENETRATING WOUNDS OF THE FOOT

Penetrating wounds of the foot are common injuries to horses used for pleasure and sport alike. Numerous objects in the horse's environment, both natural and man-made, are capable of penetrating the sole of the hoof and inflicting serious injury. Although all puncture wounds of the foot should be considered to be potentially serious, those of the central frog, palmar or plantar frog, and solar white line may be especially serious because of the consequences associated with infection of the anatomic structures immediately deep to them.

The signs of a penetrating wound may vary greatly with the severity, specific anatomic location, and chronicity of the wound. Wounds that penetrate to the level of the dermal laminae generally produce acute signs of lameness. Wounds in the central third of the frog that involve the podotrochlear bursa or deep digital flexor tendon also become rapidly symptomatic and may produce severe lameness with the development of

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osteomyelitis of the distal sesamoid bone, sepsis of the podotrochlear bursa, or septic tenosynovitis. Wounds of the sole that do not penetrate to the level of the dermal laminae and do not produce a solar fracture may not produce signs of lameness immediately. Lameness may be evident sometime later, however, if abscesses develop and migrate along the solar corium. The development of subsolar abscesses that are not actively draining is generally associated with extreme discomfort and disuse of the limb.

Horses with penetrating injuries of the foot tend to protect the affected foot by holding it forward or "pointing" the foot. When walking on the affected limb, the horse will generally demonstrate some degree of lameness. This lameness is accentuated by trotting the horse on a hard surface to increase foot concussion. Often, horses load the foot asymmetrically in an effort to reduce the degree of impact on the specific region of the injury. Horses suffering from a heel injury generally attempt to land on the toe; conversely, horses with a toe injury may attempt to land on their heel. The tendency for horses to redistribute the forces of solar concussion may lead to the development of secondary injuries in the foot. This situation is commonly observed in horses affected with pain in the palmar heel region; such individuals may acquire a secondary focus of discomfort at the apex of the frog as a result of landing on the toe to avoid landing on the heel.

Chronic injuries may present as actively draining wounds at the coronet, accompanied by varying degrees of lameness. In such cases, the entire hoof and solar surface should be evaluated for the presence of previous penetrating wounds that may have resulted in the development of a subsolar or submural abscess that subsequently drained proximal to the coronet. Penetrating wounds with established infection can also produce marked distal limb swelling. The digital flexor tendon sheath may be distended above the fetlock joint and at the palmar aspect of the pastern.

Clinical Examination

The diagnosis of penetrating wounds of the hoof is made from a review of the history and a thorough physical examination of the horse, with careful attention to the affected foot. The practitioner should inquire as to when the horse was last shod and whether any foreign objects were removed from the hoof. The foot should be cleaned to permit a complete examination for evidence of penetrating injuries, and the coronet region should be carefully examined. If a foreign body is penetrating the hoof, the object should be left in place and a radiograph taken immediately (Fig. 1). Valuable information on the depth of penetration of the object can be obtained this way. Care should be taken to ensure that deeper penetration of a foreign body does not occur while preparing the foot for radiographic examination or by the horse's weight bearing.

The solar surface and white line should be cleared with a hoof knife to facilitate the identification of regions of suspected injury. Black spots and cracks should be explored to their deepest extent to determine if they reach underlying sensitive structures. The solar surface and coronets should be palpated in an effort to identify those areas of the hoof that are warm or sensitive to digital pressure. Often it is difficult to locate tracts left by penetrating wounds of the frog. This is because the softer horn of the frog

Figure 1. View of the solar surface of the foot. A nail is penetrating the hoof at the sulcus between the sole and the frog *(arrow)*.

(compared to the sole) tends to collapse around tracts left after penetrating objects are removed. Careful evaluation by palpation, paring with a hoof knife, and hoof tester examination are necessary. Unfortunately, horses with penetrating wounds of the frog are often presented once infection is established and the individuals are severely lame. Shod horses should be examined for evidence of shoe nail encroachment within the dermal laminae. The digital pulses should be noted for intensity and symmetry. Often, a foot lesion can be localized by careful evaluation of the digital pulses by comparing the quality and intensity of the pulse within the lateral and medial digital arteries. The application of hoof testers may be useful in localizing the specific region of involvement in a suspected foot lameness. Their use should be reserved until such time as the general examination of the hoof has been completed and an appreciation of the degree of lameness has been obtained. The overzealous application of hoof testers may actually exacerbate minor pre-existing conditions such as thin soles and confuse the results of the examination. Hoof testers should be applied gently at first, as a marked pain response is generally produced when pressure is applied to sensitive septic foci. Care should be taken to apply pressure over each shoe nail or shoe nail hole if the shoe has been removed.

If infection of the distal interphalangeal joint or the digital flexor tendon sheath is suspected, paracentesis and synovial fluid analysis is

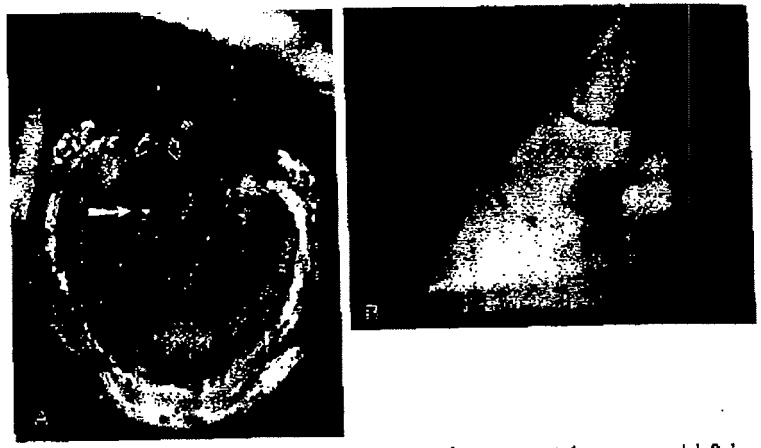

Figure 2. *A*, A teat cannula *(arrow)* is inserted into a tract *(open arrows)* left by a penetrating wound to the heel region. *B*, Lateral radiographic projection of the foot after injection of radiodense contrast medium through the teat cannula. The radiopaque contrast medium outlines the wound tract in the digital cushion.

the synovial fluid are highly suggestive of a septic process. Paracentesis should not be performed through a region of obvious cellulitis. If the digital flexor tendon sheath is distended for reasons other than infection, palpation of this region will produce no pain response, and synovial fluid will not have an elevated white cell count.

Radiographic Examination

A radiographic examination is recommended to identify foreign objects and the presence of intercurrent bony disease within the foot. The acquisition of a penetrating wound could conceivably be accompanied by additional injuries, such as distal phalanx or distal sesamoid fracture, development of phalangeal osteomyelitis, or septic arthritis of the distal interphalangeal joint. Wound tracts may be imaged by the introduction of positive-contrast agents or flexible metallic probes. Prior to invasive examination, the area should be prepared aseptically and aseptic technique employed. A metallic probe should be used with caution. The forceful introduction of a probe into a wound tract may inadvertently cause the probe to be introduced into a part of the foot previously unaffected by the initial injury. This will lead the examiner to draw false conclusions from the radiographic examination. The use of positive-contrast fistulography is preferred. A solution of the radiodense contrast agent, sodium diatrozoate, can be introduced through a teat cannula or flexible catheter positioned in the penetrating wound to evaluate the depth and extent of foot wounds (Figs. 2 and 3). At least two radiographic projections should be made perpendicular to each other, in order to appreciate the spatial relationship of probes or contrast agents to anatomic structures.[5] Radiodense foreign bodies may be visualized lodged within the foot (Fig. 4). Radiolucent

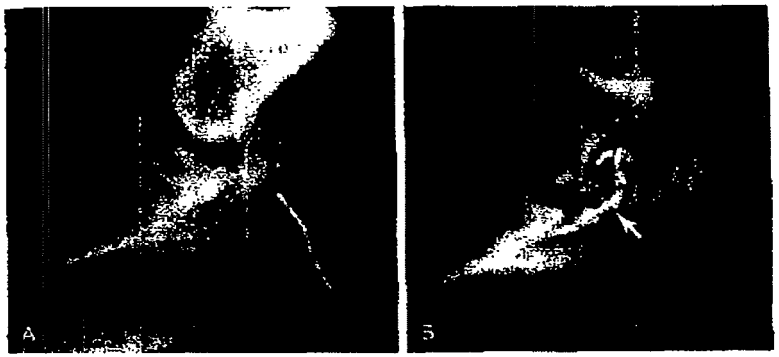

Figure 3. Lateromedial radiographic projection of the foot. *A*. A sterile, flexible, metallic probe is introduced into a penetrating wound in the heel region. The probe is close to the flexor surface of the distal sesamoid bone, but it does not confirm if the podotrochlear bursa has been entered. *B*. Contrast medium has been injected into the same wound tract occupied by the metallic probe in *A*. Contrast medium enters the podotrochlear bursa *(arrow)*.

foreign bodies will not be seen and will unlikely be defined by contrast medium in this location, since unlike radiolucent foreign bodies embedded in muscle, there is little readily displaced soft tissue in the foot. Contrast medium will not easily collect around the foreign object.

Bony changes in the distal phalanx or distal sesamoid bone often are not observed for 2 weeks or more.[6] Radiographic changes associated with distal sesamoid osteomyelitis secondary to puncture and infection of the podotrochlear bursa include destruction of the flexor cortex of the distal sesamoid bone and irregular new bone formation.[6] Pathologic fracture of the distal sesamoid bone and subluxation of the distal interphalangeal joint, associated with deep digital flexor tendon rupture (with or without rupture of the impar ligament of the distal sesamoid bone), may also be present.[6]

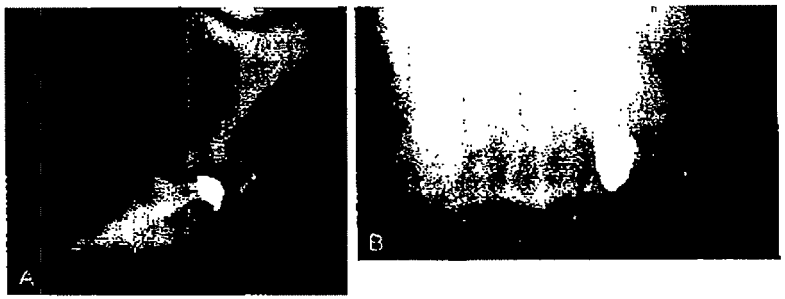

Figure 4. Lateromedial *(A)* and palmaroproximal-palmarodistal oblique *(B)* radiographic projections of the foot of a horse presented for evaluation of a penetrating injury to the heel region. Lead of a bullet *(arrow)* can be seen lodged adjacent to the distal sesamoid and distal phalanx.

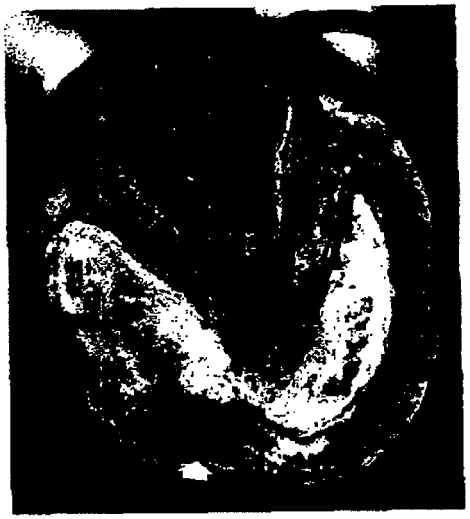

Figure 5. Solar surface of the foot. A subsolar abscess *(arrow)*, which originated from the nail hole closest to the toe, has been debrided using a hoof knife.

Treatment of Penetrating Wounds of the Foot

Treatment of penetrating wounds is generally uncomplicated if bone and synovial structures have been spared direct injury. Effective treatment requires the timely establishment of adequate drainage, debridement of necrotic or grossly infected tissues, and the application of protective dressings to permit uncomplicated resolution of the injury. Small abscesses respond rapidly to local debridement with a hoof knife (Fig. 5). More extensive infections require more debridement and supplemental therapy (Fig. 6). Drainage is established by the careful removal of undermined sole or distal hoof wall. Perineural anesthesia of the digital nerves at the level of the proximal sesamoid bones is useful to desensitize the foot and hence relieve the horse's discomfort and allow adequate debridement. Often, hypertonic dressings such as magnesium sulfate are applied to the wound to draw septic fluids out of the soft tissues of the foot. The wound is then lavaged with povidone iodine solution and dressed with a soft sterile bandage. Horses should be stalled to protect the wound from exposure to mud and environmental contaminants. The application of a vapor barrier such as foil or plastic wrap within the dressing will prevent the entry of water, urine, and fecal material into the wound.

Cases with extensive subsolar or submural involvement may benefit from daily soaking in solutions of antiseptics and magnesium sulfate. After evidence of mature granulation tissue is present in the wound, continued soaking is generally unnecessary. Astringents such as 2 per cent formalin, 2 per cent phenol, and 7 per cent tincture of iodine have been applied to these wounds as drying agents after the local exudative process has been controlled.[9] Broad-spectrum antibiotics may be administered systemically early in the treatment of these wounds until a bed of healthy granulation tissue covers the wound. Cultures of sole abscesses usually reveal a wide

Figure 6. Solar surface of the foot. An area of subsolar infection at the heel has been debrided *(open arrows)*. The debridement reached the digital cushion. Aseptic technique with the horse under general anesthesia was used. Superficial horn of the frog (F) was pared away during examination and cleaning.

variety of gram-positive and gram-negative organisms, with the preponderance of organisms being coliforms. In all cases, a review of the patient's tetanus prophylaxis is appropriate, and tetanus toxoid and antitoxin administration is indicated. Horses with resolving lesions may be shod with a shoe and pad to protect the sole as the granulation tissue matures and keratinized sole begins to develop. A solar wound should not be covered until it is dry and the patient appears to have made great improvement. Horses that are maintained on hard or rough terrain without the benefit of a stall may be shod with a boiler plate shoe (Fig. 7). The removable metal plate on the bottom of the shoe will prevent further trauma to the sole and still permit frequent removal for dressing the wound.

Deep Penetrating Wounds Involving Bone or Synovial Structures

Those penetrating injuries that have entered a bone or a synovial structure are associated with a more guarded to poor prognosis, depending on the specific structure involved and the duration of the lesion. Horses should be treated promptly. Antibiotic and anti-inflammatory therapy and tetanus prophylaxis are indicated. Immediate debridement of the wound is desirable, although horses often present with established infection of structures deep in the foot. Superficial curettage and flushing of deep puncture wounds is generally unsuccessful. Exploration of deep puncture wounds is best performed with the horse under general anesthesia and using aseptic technique. A tourniquet placed at the metacarpus or metatar-

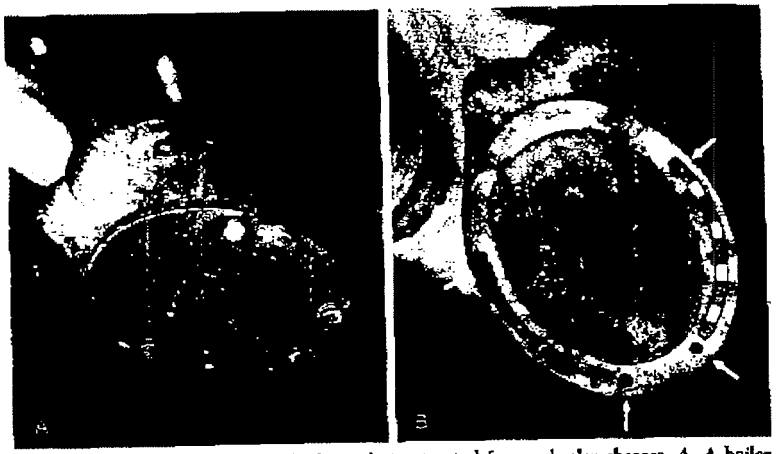

Figure 7. View of the foot of a horse being treated for a subsolar abscess. *A*, A boiler plate shoe is used to protect the sole. *B*, The metal plate of the shoe is removed by unscrewing the bolts from the threaded holes in the shoe *(arrows)* to enable inspection and care of the wound.

sus will decrease hemorrhage and facilitate surgery. Deep penetrating wounds of the sole may contact the distal phalanx. In the absence of acute radiographic changes, a localized osteomyelitis and sequestrum formation in the distal phalanx may not be diagnosed until it becomes clinically evident that the associated penetrating wound is not healing. Healing should normally take 14 to 21 days in the absence of osteomyelitis.[4] An osteomyelitis associated with a penetrating wound of 2 to 3 weeks' duration would likely have a focal radiolucency in the distal phalanx associated with the solar injury. In either case, involvement of distal phalanx in a septic process requires local decompression, debridement and curettage of the bone, and systemic antibiotic therapy and local dressings similar to those described above. Wounds in the region of the frog and bars should be dissected carefully. The gentle introduction of a sterile probe in the wound can help direct the dissection and ensure that the entire tract is removed. Dissection through the frog, corium, digital cushion, and deep digital flexor tendon to the podotrochlear bursa and distal sesamoid bone may be necessary (Fig. 8).[8] If the puncture wound is recent, fibrin may be seen in the tendon sheath or podotrochlear bursa. With chronicity, necrotic discolored tissues and roughening and discoloration of the flexor surface of the distal sesamoid bone may be apparent. During exploration, the development of a communication between the distal interphalangeal joint and the podotrochlear bursa can be assessed. A needle can be introduced into the dorsal aspect of the distal interphalangeal joint and sterile polyionic solution injected. If a communication is present, fluid will drain through the impar ligament of the distal sesamoid bone. Horses should be treated with broad-spectrum antibiotics, the choice of which should be guided by results of cytologic examination with Gram staining or culture and sensitivity

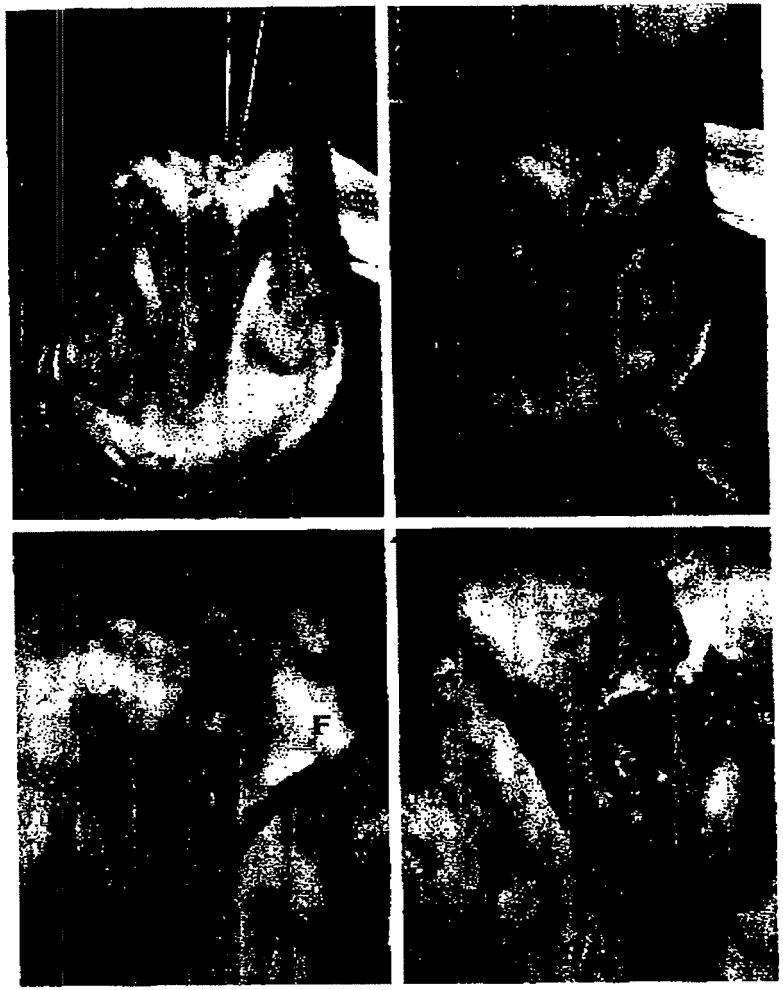

Figure 8. Exploration and debridement of the penetrating wound of the horse with lead of a bullet lodged in the foot *(illustrated in Fig 4)*. A, The foot is prepared aseptically and draped. Forceps are placed in the penetrating wound in the heel and exit through the frog. *B*, The frog over the wound tract is sharply resected. *C*, With the frog (F) reflected, exudate is seen in the corium *(arrow)*. *D*, After deeper dissection through the deep digital flexor tendon the lead of the bullet is found adjacent the distal sesamoid bone *(arrow)*.

procedures performed on tissue biopsied at the time of wound debridement. A penicillin and aminoglycoside combination is a good initial choice while awaiting sensitivity analysis.[7]

Penetrating wounds into the podotrochlear bursa have a poor prognosis. In one study, only 12 of 38 horses with puncture wounds into the podotrochlear bursa were able to return to satisfactory function.[7] Horses treated by thorough surgical debridement within one week of the injury and those with an involved hindlimb rather than forelimb had the greatest chance of survival.[7] The most common complications associated with an unsuccessful outcome included osteomyelitis of the distal sesamoid bone and rupture of the deep digital flexor tendon. Septic arthritis of the distal interphalangeal joint and fracture of the distal sesamoid bone also occurred in some cases.[7] If repeated debridement of devitalized tissue is necessary, the chance of a successful outcome is low. Surgical removal of the distal sesamoid bone as a treatment for osteomyelitis is not recommended.[7] Cancellous bone grafting to treat a defect in the distal sesamoid bone of a foal after curettage for osteomyelitis caused by a puncture wound has been described.[3]

When sepsis of the distal interphalangeal joint is present, alone or associated with puncture of the podotrochlear bursa, the joint should be lavaged with sterile polyionic solutions. If there is a clinical response to this therapy, systemic antibiotic therapy should be maintained for 3 to 4 weeks. The distinct possibility that septic arthritis would be followed by severe degenerative joint disease, even if infection is controlled, lessens the chance for a successful outcome. However, resolution of infection and ankylosis of the distal interphalangeal joint with a return to soundness can occur.

GRAVEL

Subsolar abscesses or penetrating wounds of the foot that develop a draining tract at the coronet are commonly referred to as a gravel (Fig. 9). In most instances, this condition is the result of a penetrating wound of the laminae along the white line which develops into a submural abscess and breaks and drains along the coronet. Chronic laminitis with separation and weakening of the white line (seedy toe) may also predispose to the formation of a gravel. Generally, the affected individual is lame, similar to horses with penetrating wounds or subsolar abscesses. Lameness is usually moderate to severe and often a focal area of foot pain may be localized using hoof testers. If lameness is chronic, inspection of the solar surface may be unrewarding. If the bearing surface of the hoof wall is cleaned or trimmed slightly, evidence of an old puncture wound or separation of the white line may be observed. Exploration of these areas of separation or penetration with a flexible metal probe may elicit pain or evidence of exudate. Often the diagnosis is not made until a draining tract becomes established at the coronet. Occasionally, these tracts extend from a dorsal foot injury to the palmar/plantar heel before breaking at the coronet. Radiographic examination may be used to evaluate the adjacent bony structures for evidence of osteomyelitis.

Figure 9. A draining tract at the coronet (*arrow*) associated with a penetrating wound at the white line of the sole.

Gravel is treated much the same way as other penetrating wounds of the foot. Drainage and local wound care form the basis of the typical therapeutic plan. Antibiotics may be indicted where systemic signs exist or evidence of cellulitis around the coronet is present. Chronic cases of infection tend to be effectively walled off. As with any penetrating wound of the foot, a review and appropriate boostering of the tetanus status of the patient is indicated. Cases that are identified and decompressed prior to breaking at the coronet may be curetted ventrally, treated with povidone iodine flushes, and packed in magnesium sulfate. Cases that break at the coronet may be treated in similar fashion, with the addition of periodic lavage of the tract. Refractory cases may require more aggressive therapy with hoof wall resection (Fig. 10). Once the tracts are resolved and dried, a shoe and pad may be applied. If hoof wall resection or fenestration has been required to expedite treatment, the defects may be packed with hoof acrylic.

BRUISING OF THE FOOT

Bruising can occur on any portion of the ground surface of the foot.[5] The severity of bruising can vary from hemorrhage in the solar corium (dry) to serum accumulation (moist).[9] Bruised tissue can become infected, presumably by the ingress of bacteria through cracks in the solar surface, with subsequent abscessation and necrosis of the corium (suppurating).[9] Bruising

Figure 10. Treatment of gravel by hoof wall resection. *A*, Intraoperative view after removing the hoof over the infected tract. *B*, Following resolution of infection, the exposed laminae begin to keratinize.

of the sole level with the toe or quarters of the hoof is called sole bruising. Bruising of the sole between the hoof wall and the bar is called a corn.[2]

Sole Bruises

Sole bruises result from a single traumatic event or from repetitive trauma to the solar surface of the foot and are generally seen in horses exposed to hard or rocky terrain. Particularly at risk are those horses known to have thin soles, soft soles, flat feet, or previous laminitis. Flat-footed horses have repeated concussion on the sole adjacent to the white line because the sole contacts the inner aspect of the shoe.[5] Sole bruises over the toe and quarter region are associated with a variable degree of lameness. Horses have more severe lameness when exercising on a hard surface, especially when trotting in a circle.[5] Removing the shoes generally increases the lameness. In mild to moderate cases, affected horses usually land on their heels to avoid direct concussion on the area of bruising. Severe bruising with formation of larger hematoma or serum pockets produces marked lameness. If a suppurative bruise or abscess develops, the horse may become severely lame and differential loading of the foot will no longer be observed. Examination with hoof testers is useful for identifying the exact locations of solar bruises. Regional anesthesia is sometimes required to exclude other sources of pain and lameness. After localizing the painful region of the foot, the sole is pared with a hoof knife. If the bruise is recent or located deep in the hoof, then an area of discoloration will not be seen. With old bruising, a focus of diffuse hemorrhage and discoloration may be seen within the solar horn (Fig. 11). In the absence of visual evidence of hoof bruising, the diagnosis will depend on finding localized pain in the foot, a predisposing shoeing problem or foot abnormality, and exclusion of other causes of foot lameness.[5]

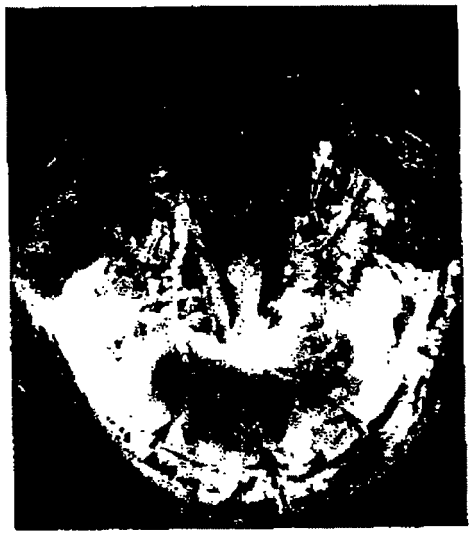

Figure 11. Solar surface of the foot after paring with a hoof knife. Bruising of the sole (discoloration) is seen (*arrows*).

Initially, sole bruises can be treated by soaking the foot in hot water and administration of anti-inflammatory drugs. Advanced serous or suppurative solar bruises are managed in a fashion similar to that described for abscesses and penetrating wounds of the foot.

Long-term treatment of sole bruises is generally achieved by instituting a program of good foot care. The affected foot should be evaluated for the presence of other disease processes such as chronic laminitis or navicular syndrome. Failure to identify the presence of such conditions complicates the management of sole bruising in that the cause of asymmetrical loading of the foot remains undetected and untreated. The horse should be rested and the housing environment altered, if possible, to reduce excessive concussion on the feet. The hoof should be trimmed to restore proper balance to the foot, and shoes with pads should be applied. In cases of chronically thin or dropped soles, the long-term application of neoprene or leather pads may be necessary to minimize further bruising. The application of shoes that have the inner solar surface ground down will eliminate the direct pressure of concussion on the sole. For this reason, they are often of value in the treatment of sole bruises in horses with thin walls or dropped or thin soles. Whenever the concavity of the sole cannot be re-established by trimming, the application of a rim pad is recommended to create a space between the solar pad and the sole. Failure to separate the pad from the solar surface may lead to continued bruising as impact forces are transmitted through the pad and into the sole.

The prognosis is good for horses with foot bruising caused by a single traumatic episode and for horses with good foot conformation. Horses that have flat soles or underrun heels that are to be used on hard ground have

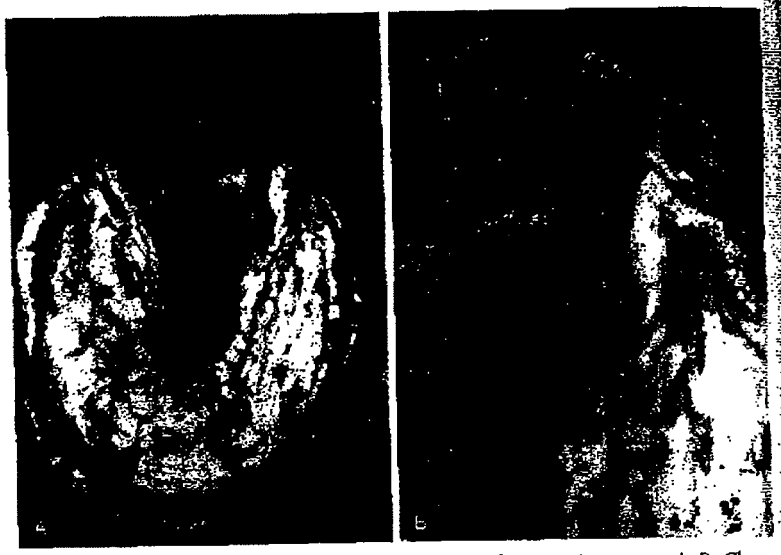

Figure 12. A, Solar surface of the foot of a horse with a corn *(open arrow)*. B, Closer view of the angle of the sole in A showing the hemorrhage (discoloration) *(arrows)* in the horn of the sole.

a guarded prognosis because secondary, chronic problems such as pedal osteitis can develop.[9]

Corns

Corns usually result from poor foot conformation or improper shoeing.[3] While corns are an unusual finding in unshod horses, a long toe and short medial quarter or heel may lead to excessive differential loading of the medial bar and heel, ultimately resulting in formation of a corn.[3] The most frequent location of corns is the medial heel of the forelimb; however, they may occur laterally and in the hindlimb (Fig. 12).

Various types of shoeing and hoof trimming may put a horse at risk for developing a corn. The underlying problem is that the sole at the heel, and not the adjacent hoof wall, is receiving pressure during weight bearing.[3] Farriers commonly bend the inside branch of a shoe towards the frog to prevent a horse from stepping ahead with a hindlimb and pulling the shoe off the forelimb.[9] Unfortunately, this places the shoe in contact with the sole and not the wall. Repetitive concussion can result in bruising of the sole in contact with the shoe.[5] If a shoe is left on too long the same effect develops as the hoof outgrows the margins of the shoe and the sole at the heel makes contact with the shoe.

Horses with long toes and short underrun heels put more pressure on the heel region. If shod with a shoe that is one half to a full size too small, the problem is exacerbated.[3] Sometimes correction of gait or conformation

abnormalities utilizes shoes that create foot imbalance. This is especially a problem when one heel is wedged, a heel calk is used on one side, or heel calks are of unequal length.[5] Such corrective shoeing concentrates forces onto one heel during weight bearing and a corn can result. Loose shoes can shift to make contact with the sole and cause bruising. Horses with flat-soled feet are at greater risk because the sole is in contact with the shoe and minor faults in shoeing result in increased sole pressure.

Horses with corns have varying severity of lameness. Sometimes signs are only apparent when horses are worked on hard surfaces. Trainers may present horses with a history of being short strided when exercised on firm ground but stretching out in soft conditions. Affected horses tend to land on the toe to reduce the pressure on the affected heel and may have a clinical appearance similar to other conditions of the foot, including navicular syndrome, type I distal phalangeal fractures, or sheared heels.[5] Inspection of the foot may reveal improper shoeing or trimming as discussed above. Hoof tester examination reveals variable discomfort when pressure is applied to the affected heel. Unilateral perineural anesthesia of the palmar digital nerve should relieve lameness in the case of a unilateral corn. When the superficial horn of the sole is pared away with a hoof knife, red or bluish discoloration of the hoof may be seen. Corns can develop into foot abscesses.

If a corn is extensive or deep, then much of the involved horn should be removed with a hoof knife.[3] Removal of hoof over and involved in the corn often provides some relief of discomfort. However, it is not necessary to remove much of the sole unless a serous or suppurative corn is present. In the case of a large serous or suppurative corn, the lesion should be debrided, dressed, and treated in a fashion similar to that of a severe bruise, abscess, or penetrating wound of the foot. Hot water foot soaks and anti-inflammatory medication help provide short-term relief.

Faults in hoof trimming and shoeing that may have produced the corn should be corrected. Long toes should be trimmed. The wall at the heel should be left to grow if the heels are underrun. Wide-web shoes that do not extend to the sole should be used. If the corn was extensive, a shoe that is deeply concaved with the concavity facing the ground surface of the hoof at the site of the corn can be used.[3, 4] This will prevent continued pressure on the affected area during weight bearing.

The prognosis for resolution of a corn is good if major conformational abnormalities of the foot are not present. If the corn was produced by a singular event, such as a loose shoe or lodging of a foreign object in the heel, the prognosis is also good.[5] If the horse has poor hoof conformation and is to be used on hard or rough ground, the prognosis is guarded because of the potential for chronic problems.

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Management of Lacerations and Avulsion Injuries of the Foot and Pastern Region and Hoof Wall Cracks

*T. S. Stashak, DVM, MS**

Because of their distal locations on the limb, the foot and pastern regions are particularly susceptible to trauma. Laceration and avulsion injuries commonly are caused by barbed wire or kicking at or stepping on sharp objects. These injuries occasionally occur as a result of the foot becoming entrapped (for example, in a large metal can). Hoof wall cracks can develop from either laceration or avulsion injuries of the foot, excessive dryness, imbalanced feet, letting the feet grow too long, or tearing of the hoof by improper shoe removal or loose shoes. Because the foot and pastern regions are close to the ground, open wounds frequently become contaminated with feces, urine, and dirt and subsequently become infected. With proper treatment, however, many of these injuries can heal completely. The hoof wall can reform all its components, including the coronary band, but it usually takes longer than other regions because wound contraction is limited. Healing primarily is by epithelialization. Additionally, because growth of the hoof wall is from the stratum germinativum of the coronary epidermis toward the ground, reformation of the hoof wall (without a defect) can occur if the coronary epidermis is intact or it has healed by epithelialization. If the coronary corium (dermis) also is injured, imperfect, but often functional, hoof wall may develop. The specific treatments recommended for each of these injuries and prognosis will be covered under the separate topic headings.

LACERATIONS OF THE PASTERN

Lacerations of the pastern region frequently involve the coronary band and variable portions of the hoof wall and, depending on their depth, may involve structures deep to the hoof wall. The heel bulb region appears to

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SECTION • 1
Traditional Therapy

CHAPTER • 85

Principles and Practices of Joint Disease Treatment

John P. Caron and Ronald L. Genovese

Recent advances reveal that osteoarthritis is a dynamic process, unlike previous concepts of a passive wear-and-tear phenomenon. Although many questions remain unanswered, our understanding of the pathophysiology of osteoarthritis and biological effects of therapeutic agents has expanded. Technical improvements in imaging modalities and arthroscopic surgical techniques allow early diagnosis and have broadened our perspective, paving the way for future progress in managing equine osteoarthritis.

MEDICAL TREATMENT

Pain (lameness) is the main reason most horses are examined, and rapid resolution of signs is the principal concern of most owners and trainers. Ideally, medical management of osteoarthritis would serve to arrest or at least slow the progression of lesions, a treatment objective termed *chondroprotection* or *disease modification*. Several factors influence therapeutic decisions in the medical management of osteoarthritis in horses, including the following:

1. The specific joint involved
2. The stage of osteoarthritis
3. The current and intended use of the horse
4. The age of the horse
5. Regulations governing anti-inflammatory medication use in competition
6. Treatment cost
7. Response to therapy

Therapeutic decision making also is complicated by the inherent nature of osteoarthritis, a condition that progresses at a variable rate and with signs difficult to quantify. Also, important degenerative changes and structural damage of cartilage matrix may precede the development of clinical signs, and late diagnosis precludes the possibility for complete resolution. Variability in response of horses with similar lesions supports the contention that osteoarthritis is a spectrum of disease. Despite recent progress, established osteoarthritis is incurable and frequently limits the serviceability of affected horses.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are agents that inhibit one or more reactions involved in the production of prostaglandins and thromboxanes. Prostaglandins, particularly those of the E series, are associated with synovial inflammation and cartilage matrix depletion,[1,2] and although the specific effects of prostaglandins on joint metabolism are unclear, it is widely believed that prostaglandin E_2 plays a role in processes leading to joint degeneration. Prostaglandin E_2 has been demonstrated in the synovial fluid of horses with osteoarthritis,[3] and in vitro studies indicate that synoviocytes and chondrocytes synthesize prostaglandin E_2 after exposure to other inflammatory mediators.[4-6] Prostaglandin E_2 was implicated in the erosion of cartilage and adjacent bone,[7] and other studies suggest that prostaglandins may modulate latent metalloproteinase release and subsequent cartilage matrix degradation.[8,9] Paradoxically, reports suggest that matrix metalloproteinase expression in human synovial fibroblasts is inhibited by E-series prostaglandins.[10] These and other data suggest that prostaglandin E_2 may serve a regulatory function in inflamed joints and inhibition may not produce uniformly favorable results.[11] Thus recent evidence suggests that prostaglandin inhibition, although effective in providing symptomatic relief, may have deleterious effects on cartilage metabolism in the long term.[12] Establishing the specific biological effects of prostaglandin E_2 and the consequences of its inhibition in the equine joint is important, given the widespread use of NSAIDs in osteoarthritis treatment and the recognized toxic side effects that can result.

The principal action of most NSAIDs is the inhibition of cyclooxygenase (COX), the first in a series of enzymes responsible for converting arachidonic acid to prostaglandins (Fig. 85-1). Importantly, two forms of COX exist: the first produces physiological levels of prostaglandins in a constitutive manner (COX 1) and the second, an inducible form of the enzyme (COX 2), is responsible for the elevated levels of

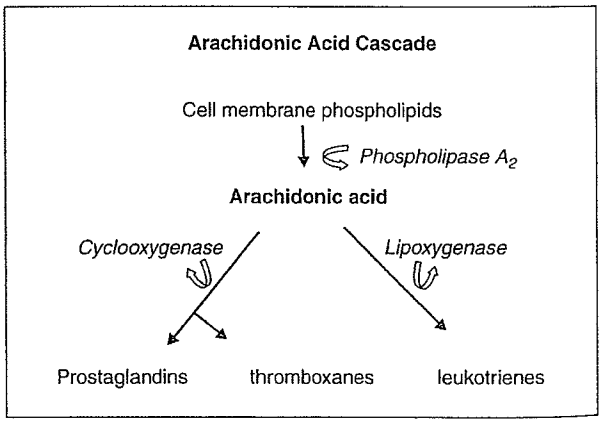

Fig. 85-1 Arachidonic acid cascade. Common therapeutic targets include phospholipase A_2 (corticosteroids) and cyclooxygenase (corticosteroids and non-steroidal anti-inflammatory drugs). Prostaglandins, particularly those of the E series, are associated with synovial inflammation and cartilage matrix depletion; however, accumulating evidence indicates that prostaglandin E_2 plays a role in regulating over-production of proteolytic enzymes by articular chondrocytes.

prostaglandins observed during inflammatory events.[13,14] The constitutive activity of COX 1 is responsible for many of the homeostatic properties ascribed to prostaglandins and toxicity is related to sustained COX 1 inhibition.[15,16] Most currently available NSAIDs inhibit the activities of both COX isoforms. However, the proportionate inhibition of COX 1 to COX 2 varies among compounds, and many aspects of the specific anti-inflammatory profiles of most NSAIDs used in horses remain to be explored in detail. A number of selective COX 2 inhibitors have been approved recently for use in people and to date have similar clinical efficacy to that of non-specific COX inhibitors, largely unaccompanied by typical NSAID side effects.[17-19] COX 2 inhibitors have been introduced to companion animal practice and likely will soon find use in horses, particularly when more affordable generic forms become available. This development may address existing problems with toxicity and potential unfavorable effects on cartilage metabolism of currently used NSAIDs.[20-22]

In addition to COX inhibition, NSAIDs have other anti-inflammatory effects. For example, carprofen reduces edema and effusion in experimental osteoarthritis in horses by a non–COX-mediated pathway.[23] Ketoprofen inhibits lipoxygenase and COX.[24] Moreover, at least some NSAIDs are capable of inhibiting elements of cellular inflammation.[25,26] Thus it is clear that at least some NSAIDs possess anti-inflammatory actions other than COX inhibition, although the biological significance of these effects is uncertain and may occur only at tissue concentrations achieved by exceeding normal dosages. These side actions may complicate the premise that selective COX 2 inhibitors are devoid of side effects, particularly when used at higher dosages where effects unrelated to COX inhibition are evident.

Pain relief from NSAIDs is mainly, but not exclusively, related to COX inhibition. Prostaglandins do not produce pain, except when present in large quantity.[27] Prostaglandin E_2 sensitizes peripheral nerve endings to mechanical stimuli and amplifies the chemical activation of pain receptors by other inflammatory mediators such as bradykinin and histamine, both of which act to lower the pain threshold.[28,29] Reducing prostaglandin levels also appears to modulate pain perception centrally, at the level of spinal receptors distant from sites of inflammation.[30] In addition to COX inhibition, certain NSAIDs possess other mechanisms of analgesia, because COX inhibitory activity of some compounds is not correlated closely with analgesic potency.[31] For example, the R-enantiomer of flurbiprofen is a weak COX inhibitor compared with its D-enantiomer, but it has comparable analgesic potency.[32] Among other ancillary mechanisms, NSAIDs may contribute to analgesia by inhibiting sensory neurotransmitter synthesis at a spinal level.[33]

At present, phenylbutazone is the least expensive and most popular agent used in horses, and its clinical efficacy appears to compare favorably with other NSAIDs.[34] (Table 85-1). Other choices include flunixin meglumine, meclofenamic acid, naproxen, ketoprofen, and carprofen, for which the basic pharmacology in horses was recently reviewed.[35,36] It should be noted that considerable variation exists in the pharmacokinetic profiles of NSAIDs among horses, and clearance is influenced by a variety of factors such as dose, the presence or absence local inflammatory conditions, and feeding schedule (for orally administered drugs).[37-40] The latter effect can be a consideration in estimating withdrawal times, given that the peak plasma concentration and apparent half-life can be substantially delayed when NSAIDs are given to horses with

Table • 85-1

Non-Steroidal Anti-Inflammatory Drugs Used to Treat Musculoskeletal Pain

GENERIC NAME	TRADE NAME(S)	FORMULATION(S)	RECOMMENDED DOSE (mg/kg)	RELATIVE PRICE (per day)
Phenylbutazone*	Phenylbutazone injection Bizolin 200 Equipalazone Equiphen paste etc.	Tablets Paste Granules/powder Injectable (IV only)	4.4 bid 1, 2.2 bid (4 days), then 2.2 sid (IV, PO)	(Dose is 2.2. mg/kg bid) Tablets (1 g) = 1.0 Paste (12 g) = 2.8 Injectable = 6.9
Flunixin meglumine†	Banamine Citation Meflosyl, etc.	Granules Paste	1.1 daily for 5 days (IV, IM, PO)	(Dose is 1.1 mg/kg sid) Granules (500 mg envelope) = 5.0 Paste (1500 mg tube) = 12.4 Injectable (50 mg/ml) = 6.8
Meclofenamic acid†	Arquel	Granules	2.2 sid (5-7 days), then 2.2 sid or less (PO)	(Dose is 2.2 mg/kg sid) Granules = 1.6
Naproxen†	NM	Tablets	10 sid for up to 14 days (PO)	(Dose is 10 mg/kg sid) Tablets (500 mg) = 7.1
Ketoprofen†	Ketofen	Injectable	2.2 sid (IV)	(Dose is 2.2 mg/kg sid) Injectable (100 mg/ml) = 27.4
Carprofen†	Rimadyl‡	Injectable	0.7 sid (IV)	(Dose is 0.7 mg/kg sid) Tablets (100 mg) = 4.2

NM, Not currently marketed by veterinary distributors in the United States.
*Enolic acid.
†Carboxylic acid.
‡Only available in tablet form in the United States.

access to hay. Dose rates and schedules may have to be adjusted for individual horses to accommodate these effects.

The chondroprotective (and potential deleterious) effects of NSAIDs have been investigated in vitro, although the clinical relevance of the results is not clear. Certain NSAIDs are known to inhibit anabolic activities in chondrocytes, whereas others stimulate matrix synthesis.[41-44] Concern over the potential unfavorable side effects of these agents began with the observation that aspirin inhibited proteoglycan synthesis and could encourage cartilage destruction[45,46] and that ibuprofen was implicated in accelerated joint destruction in people with osteoarthritis.[47,48] Fears of enhanced rates of cartilage degradation with NSAID use were not borne out in a number of clinical and experimental studies.[49,50] In vitro data may not parallel ex vivo data in the same species. For example, indomethacin reduces proteoglycan synthesis in canine cartilage explants; however, cartilage obtained from indomethacin-treated and control dogs had similar synthetic rates.[44] Indeed, certain NSAIDs have shown to be chondroprotective in some osteoarthritis models.[51-53]

Similar to the effects on cartilage matrix synthesis, NSAIDs vary in the ability to inhibit both catabolic events in cartilage and the effects of degradative enzyme activity.[54] Although many studies have focused on direct inhibition of degradative enzymes, NSAIDs may be of benefit by suppressing other mediators.[55,56] For example, in one of the few equine studies, phenylbutazone limited proteoglycan depletion that accompanies in vitro culture of articular cartilage,[57] but the effect was not mediated by stromelysin inhibition.[58]

Corticosteroids

Corticosteroids are the most potent anti-inflammatory agents used to treat osteoarthritis. Normally injected directly into affected joints, corticosteroids depress numerous inflammatory processes, including capillary dilatation; margination, migration, and accumulation of inflammatory cells; and liberation of enzymes, cytokines, and other inflammatory mediators.[59,60] Notably corticosteroids also inhibit prostaglandin production by inhibiting phospholipase A_2 and COX 2 (but not COX 1).[61] The consequence of inhibiting arachidonic acid metabolism is a rapid and pronounced reduction in pain.

A long-standing controversy surrounds the use of corticosteroids in treating osteoarthritis because of the concern that overuse of a pain-free joint could result in accelerated degeneration.[62-64] This impression has been compounded by demonstrated negative effects of corticosteroids on chondrocyte metabolism. Particularly at high concentrations, corticosteroids inhibit proteoglycan synthesis and unfavorably influence the structural organization of cartilage collagens, even in normal cartilage.[65-70] Conversely, other studies have demonstrated that corticosteroids have certain chondroprotective properties. At low doses, they are capable of inhibiting the process of cartilage degradation by inhibitory effects on the synthesis of matrix metalloproteinases (MMPs) and cytokines[71-73] These in vitro data are supported by results in animal models demonstrating cartilage-sparing effects of low-dose corticosteroids, without significant effects on chondrocyte health.[74-76] It is well established that corticosteroids inhibit the gene expression of MMPs; however, this effect must be weighed against a similar effect on the expression of the natural inhibitory protein of these enzymes (tissue inhibitor of matrix metalloproteinase, or TIMP) and matrix collagen and proteoglycan synthesis.[77,78] The magnitude and relative contributions of these inhibitory effects need to be defined more fully, although it may be possible to determine a concentration of drug that produces chondroprotective effects while minimizing negative consequences on chondrocyte anabolic activity.

Although proteoglycan depletion with high doses of corticosteroids is an incontestable phenomenon, its importance as a clinical entity is contentious.[79-81] Noteworthy are recent studies using horses with iatrogenic osteochondral lesions of the carpus treated with betamethasone and triamcinolone acetonide. After treatment horses were exercised on a treadmill. Lesions of cartilage and bone in treated horses were comparable to those in controls.[82,83] To investigate the possibility that different corticosteroid preparations may exert varied effects on joint metabolism, a similar protocol was conducted by the same research group, using methylprednisolone acetate. In this study, morphological lesions were observed that the authors considered related to corticosteroids.[84] It should be noted that, as in other studies evincing unfavorable effects of methylprednisolone acetate, the dose used (100 mg the first and fourteenth days) would be considered generous by current standards. Additionally, the effects of methylprednisolone acetate on chondrocyte metabolism differ between normal and inflamed joints. In inflamed joints modest concentrations of methylprednisolone acetate may have less dramatic effects on matrix synthesis than in normal joints.[85] In summary, although intra-articular use of corticosteroids may potentially aggravate existing cartilaginous lesions, the potential deleterious effects are overemphasized.

The type, dose, and frequency of corticosteroid administration remain subjective. Common choices and dose ranges are given in Table 85-2. In general, pharmacokinetic data suggest that corticosteroid suspensions have short intra-articular half-lives.[86-88] Considerable variation in the clearance of corticosteroid suspensions exists. For example, the active moiety of methylprednisolone acetate can be liberated for up to 1 month.[89] The specific reasons for divergent pharmacokinetic profiles and the duration of anti-inflammatory effect far exceeding intra-articular half-life of corticosteroids are unclear.

Table 85-2

Corticosteroid Suspensions Used Intra-Articularly

CORTICOSTEROID	TRADE NAME	MANUFACTURER	CONCENTRATION (mg/ml)	DOSE (mg)*	POTENCY RELATIVE TO HYDROCORTISONE
Betamethasone sulfate	Celestone Soluspan	Schering-Plough	6†	3-18	30
Triamcinolone acetonide	Vetalog	Solvay	6	6-18	5
Flumethasone	Flucort	Syntex	0.5	1.25-2.5	120
Isoflupredone acetate	Predef 2X	Pharmacia and Upjohn	2	5-20	50
Methylprednisolone acetate	Depo Medrol	Pharmacia and Upjohn	40	40-120	5

*Dose ranges are somewhat arbitrary. Magnitude and duration of clinical effects vary widely.
†Each milliliter contains betamethasone acetate (3 mg) and betamethasone sodium phosphate (3 mg).

Most clinicians currently use lower doses of corticosteroids than their predecessors, because the dose-dependent deleterious effects are now recognized and most are now aware that favorable response is achieved using lower doses. For example, intra-articular injection of 120 to 200 mg of methylprednisolone acetate was commonplace years ago, but now it is performed using 10 to 40 mg, depending on the specific joint involved. Another popular and potentially beneficial practice is the co-administration of a low dose of a depo-corticosteroid and hyaluronan. Therapeutic synergy was reported for people with osteoarthritis, and a similar effect in horses is possible.[90] Many veterinarians (and trainers) find the idea of combination therapy appealing, because the corticosteroid dose can be reduced and it can be combined with the putative cartilage-sparing effect of hyaluronan. The minor risk of infectious arthritis exists with any intra-articular injection, and after intra-articular corticosteroids, signs of infection may be delayed from the potent anti-inflammatory effects of these preparations.[91]

Hyaluronan (Sodium Hyaluronate)

Hyaluronan is a glycosaminoglycan composed of the disaccharides D-glucuronic acid and *N*-acetyl-*D*-glucosamine. This glycosaminoglycan is an important component of articular cartilage, where it plays a major role in forming proteoglycan aggregates. The viscoelasticity of synovial fluid is due to its rich hyaluronan content and this molecule serves as the principal lubricant of synovial soft tissues. These physical properties, along with other incompletely characterized pharmacological effects, help maintain synovial homeostasis. The biological characteristics and therapeutic use of hyaluronan in equine osteoarthritis have been reviewed.[92] Characteristics of hyaluronan formulations are summarized in Table 85-3.

Despite not knowing the specific mode(s) of action, hyaluronan frequently is used to treat osteoarthritis in people and horses. Documented clinical benefits after intra-articular injection in people include reduced pain and improved joint mobility,[93,94] and effects compare favorably with NSAIDs and corticosteroids.[90,95] Most equine studies report beneficial effects, but most lack appropriate controls and outcome criteria and are subjective.[96-98]

Hyaluronan has modest analgesic effects,[99] but it has mostly anti-inflammatory effects that may be physical (steric hindrance) or pharmacological (inhibition of inflammatory cells and mediators).[100-104] Symptomatic improvement can be dramatic. In an ovine osteoarthritis model, cartilage lesions in hyaluronan-treated animals were attributed to excessive limb use.[105-107] Hyaluronan may improve range of motion by improving synovial fluid viscosity and soft tissue lubrication. In osteoarthritis, reduced joint excursion may be caused in part by the dilution and depolymerization of endogenous hyaluronan that accompanies synovitis.[108-110]

The specific effects of hyaluronan on articular metabolism remain unclear. Exogenous hyaluronan may stimulate synthesis of a highly polymerized endogenous form of hyaluronan by synoviocytes, but evidence was lacking in studies using cultured synovial fibroblasts derived from normal equine joints or those from joints with osteochondral fragments.[111] Hyaluronan stimulates proteoglycan synthesis by equine chondrocytes.[112] In vitro, hyaluronan is protective for cartilage matrix loss induced by interleukin-1.[113-115] Recent studies have revealed that hyaluronan regulates the production of prostaglandins by articular cells and can protect cartilage against the effects of oxygen-derived free radicals and degradative enzymes.[102,103,116-118] However, compelling evidence for the ability of hyaluronan to inhibit the activity of MMPs has not been reported to date.[111,119] Interestingly, a number of studies have demonstrated that several inflammatory mediators, including prostaglandins, interferon, and certain protein factors, can augment the production of hyaluronan by synovial fibroblasts in vitro.[120,121] Therefore elevated synthesis of hyaluronan in early osteoarthritis may constitute a protective response by the synovium to joint inflammation, providing a rationale for exogenous administration. Like corticosteroids, the protracted pharmacodynamic

Table 85-3

Common Hyaluronan Preparations Used in Horses

TRADE NAME	MANUFACTURER	CONCENTRATION	MOLECULAR WEIGHT (IN DALTONS, FROM MANUFACTURER)	HOW SUPPLIED	RECOMMENDED DOSE*
Hylartin V (Hylartil Vet)	Pharmacia and Upjohn	10 mg/ml	3.5×10^6	2-ml syringe	20 mg
MAP-5	Vetrepharm	10.3 mg/ml (2 ml) 5 mg/ml (10 ml)	7.5×10^5	2-ml vial 10-ml vial	20 mg†
Hycoat	Neogen	5 mg/ml	$>1.0 \times 10^6$	6-ml vial	30 mg‡
Hyvisc	Vetmedica	11 mg/ml	2.1×10^6	2-ml syringe	20 mg
HY-50	Bexco Pharma	17 mg/ml		3-ml syringe	51 mg
Equron	Solvay Animal Health	5 mg/ml	$1.5\text{-}2.0 \times 10^6$	2-ml syringe	10 mg
Equiflex	Chesapeake Biological	5 mg/ml	1×10^6	5-ml vial	10 mg
Synacid	Schering-Plough	10 mg/ml	$0.15\text{-}0.20 \times 10^6$	5-ml vial	50 mg
Hyalovet (Hyalovet-20)	Fort Dodge/ Vetrepharm	10 mg/ml	$4\text{-}7 \times 10^5$	2-ml syringe	20 mg
Legend (Hyonate)§	Bayer Corporation	10 mg/ml	3×10^5	4-ml vial	40 mg (IV)

*Intra-articular dosages are those recommended for small- to medium-size joints (e.g., metacarpophalangeal). Some manufacturers recommend twice the dose for larger joints (e.g., tibiotarsal).
†Marketed as an ophthalmic preparation but popular for intra-articular use at this dose.
‡Marketed as a topical preparation for wounds but used intra-articularly.
§Marketed for both intravenous and intra-articular use.

influences of exogenously administered hyaluronan are attributable to indirect effects on synovial and cartilage metabolism, because intra-articular half-life is only several hours in normal joints[122,123] and is further reduced in synovitis.[124] Favorable in vitro effects of hyaluronan are supported by observations of cartilage-sparing effects after intra-articular administration of hyaluronan in animal models of arthritis.[106,107,125-128]

Hyaluronan preparations of a molecular weight exceeding 1×10^6 d may provide superior clinical and chondroprotective effects, although this claim is controversial.[129] Certainly, many potentially beneficial effects observed in vitro depend on molecular weight,[99,103,108,118] but whether these effects occur in vivo is unclear. Cartilage-sparing properties of a high molecular weight hyaluronan were superior to those of a less polymerized preparation in rabbits in a limb immobilization model,[128] and better clinical results in horses were reported when using hyaluronan exceeding 1×10^6 d, rather than lower molecular weight formulations.[130,131] Conversely, others maintain clinical efficacy is related to the purity of the preparation, rather than molecular weight.[98,132]

Recently a form of hyaluronan intended for intravenous use has become available. The precise mechanisms of action are uncertain, but beneficial clinical and biochemical effects were observed in an equine lameness model,[133] suggesting that the product need not cross the blood-synovial barrier to exert its action(s). When used in horses with synovitis, intravenous hyaluronan appears to decrease lameness and synovial effusion. Recent studies have demonstrated that hyaluronan receptors exist on numerous extra-articular cell types, and if involved with joint inflammation, intravenous hyaluronan may exert a positive effect.[134,135]

In the horse, hyaluronan appears to be most effective in treating acute synovitis, and results when used in more advanced disease are frequently disappointing. The frequency of hyaluronan administration for the treatment of osteoarthritis in people (often weekly) is higher than that typically used in the horse. Optimal results in horses may require more frequent injections than routinely recommended, particularly in those with established joint lesions. Although often heralded as being virtually free from side effects, data from animal models suggest that despite its putative chondroprotective properties, continued joint deterioration in treated animals may occur when the primary cause of osteoarthritis remains uncorrected.[105-107]

Polysulfated Glycosaminoglycan

Polysulfated glycosaminoglycan (PSGAG) is a semi-synthetic preparation from bovine trachea, comprised principally of chondroitin sulfate, a glycosaminoglycan found in the aggregating proteoglycan of cartilage. The molecular weight of PSGAG varies between 2 and 16 kd; the mean molecular weight is 6 kd. PSGAG is purported to have chondroprotective and anti-inflammatory properties; however, the exact nature and mechanism(s) by which it exerts these effects are unknown. Thorough reviews of the biological properties and clinical use of PSGAG are available in the veterinary literature.[136,137]

PSGAG reduces the severity of clinical signs in people and horses with arthritis.[138-143] Clinical improvement is likely attributable to anti-inflammatory effects, including the inhibition of prostaglandin E_2 synthesis and inhibition of cytokine release.[117,144,145]

PSGAG is reported to have numerous favorable effects on joint metabolism, including stimulation of hyaluronan production by synoviocytes and synthesis of proteoglycans and collagen by chondrocytes.[146-149] The latter effects are thought to be more pronounced in arthritic cartilage.[149] Despite the existence of in vitro studies supporting anabolic properties of PSGAG, subsequent research has questioned modes of action, particularly PSGAG putative stimulation of cartilage proteoglycan synthesis. Dramatic stimulatory effects on chondrocyte biosynthesis were not clearly demonstrable in studies using equine cartilage explants, particularly those in which normal or mildly osteoarthritic cartilage was used.[150,151] An anabolic response may be more evident in chondrocytes from joints with significantly deranged cartilage metabolism,[149] but clinical benefit of such response is questionable. Moreover, PSGAG has limited effects on the early healing of cartilage lesions, and repair tissue formed in healing cartilage wounds under the influence of PSGAG may be inferior to that in untreated animals.[152,153]

Although the nature and magnitude of its anabolic effects are unclear, PSGAG is widely held to have anti-catabolic effects. PSGAG is capable of inhibiting the activity of a number of degradative enzymes known to be present in articular tissues, including elastase, some cathepsins, serine proteases, and neutral MMPs.[58,136,137,154-156] Mechanisms of enzymatic suppression are characterized incompletely, but they may include direct inhibition or abrogation of the synthesis or activity of other mediators that stimulate degradative enzyme release. For example, our recent data (J.P.C.) indicate that PSGAG inhibits inducible nitric oxide synthase expression and synthesis in cytokine-stimulated equine chondrocytes in culture. A variety of animal models of arthritis have provided support for a cartilage-sparing effect of PSGAG in vivo,[153,157-160] and in most cases beneficial effects were attributed mainly to the inhibition of degradative enzymes.[155,160]

PSGAGs can be administered intra-articularly or intramuscularly, but slight risk of infection (quantitatively exceeding that of corticosteroids) with intra-articular administration of PSGAGs has reduced enthusiasm for this route.[161] Most clinicians now combine an aminoglycoside (e.g., amikacin, 125 mg) with PSGAG as a preventative measure. Articular cartilage concentrations of PSGAG after intramuscular administration are capable of inhibiting some cartilage-degrading enzymes,[162] yet the duration of a persistent effective concentration is unclear. As for other anti-arthritis preparations, the frequency of administration of PSGAG usually is based on the therapeutic response and its duration. Typically, when a favorable therapeutic response occurs, it is rapid. For intramuscular use the manufacturer recommends that PSGAG be given at a dose of 500 mg every 4 days for 28 days. Clinical experience suggests that if improvement is not evident within 7 to 10 days using this schedule, a dramatic response from subsequent injections is unlikely.

Pentosan Polysulfate

Pentosan polysulfate is a compound prepared by sulfation of beechwood hemicellulose, consisting of xylopyranose chains, to which are attached methylated glucuronyl rings at regular intervals. Like PSGAG, pentosan polysulfate is a highly sulfated molecule, a property that likely contributes to its biological activity.

Pentosan polysulfate appears to have chondroprotective effects similar to PSGAG, including promotion of anabolic activity of chondrocytes and synoviocytes and inhibition of degradative enzymes.[163,164] Studies using animal models support these chondroprotective effects.[161,163,165,166] Pentosan polysulfate is not presently available in North America but is approved for use in Australia, and anecdotally, pentosan polysulfate is effective in reducing lameness in racehorses with chronic osteoarthritis.[163] Experienced clinicians report pentosan polysulfate provides symptomatic relief in some horses that have been unresponsive to PSGAG. The recommended dosage regimen is 2 to 3 mg/kg intramuscularly every 7 days for 28 days, and the series can be repeated every 3 months as required.[163] Further clinical experience with pentosan polysulfate is required to define specific indications.

Glucosamine and Chondroitin Sulfate

Glucosamine and chondroitin sulfate are compounds extracted from animal products that have been used to treat osteoarthritis in people in Europe for more than a decade. In North America an interest in using these products in people and animals has developed. These supplements reportedly possess anti-inflammatory and disease-modifying effects, and because of the relative safety, they could have great use in managing osteoarthritis even if they are only modestly effective. In vitro and appropriately designed and rigorous clinical trials are lacking, but available data suggest beneficial effects.

Glucosamine sulfate is a precursor of the disaccharide subunits of cartilage proteoglycans. Glucosamine salts appear to be well absorbed after oral administration.[167] In vitro studies indicate that glucosamine sulfate increases proteoglycan synthesis by chondrocytes and may have a number of anti-inflammatory activities.[168-171] Glucosamine was protective for proteoglycan loss and inhibited MMP synthesis and activity in equine cartilage explants.[172] Follow-up experiments using a variety of glucosamine derivatives and sulfated glucose controls demonstrated that cartilage-sparing properties of glucosamine are shared by the 3-sulfate and hydrochloride salts but that glucose-3-sulfate and *N*-acetylglucosamine are devoid of chondroprotective effects at equimolar doses.[173] Glucosamine also appears to reduce the suppressive effects of some cytokines on cartilage proteoglycan synthesis.[174] The hydrochloride salt of glucosamine is less expensive than the sulfated forms and constitutes the principal form of glucosamine marketed in North America.

Chondroitin sulfate consists of chains of sulfated galactosamine and glucuronic acid molecules and is the principal glycosaminoglycan of aggregating proteoglycan (aggrecan). Chondroitin sulfate is less sulfated but resembles PSGAG in structure and mechanisms of acton. Data from in vitro studies have demonstrated anti-inflammatory properties of the drug on leukocytes.[175] Experiments have provided evidence of chondroprotective effects of chondroitin sulfate, including stimulating the synthesis of proteoglycans and inhibiting the activity of certain matrix degrading enzymes, particularly when chondroitin sulfate is present in a polymerized or long-chain form.[176-178] Chondroitin sulfate also has protective effects for cartilage proteoglycan loss in animal models of joint inflammation.[179,180]

Controversy persists regarding the efficacy of enteral absorption of chondroitin sulfate in a biologically active (long-chain) form. In monogastric species, the oral bioavailability is less than 20%,[175] and although isotope recovery is possible in animals fed radiolabeled chondroitin sulfate,[181] absorbed radioactivity may reside in small-chain or monomeric forms of the sugar that lack the biological effects of polymers.[182] Gastrointestinal absorption of polymerized chondroitin sulfate in the horse is unknown.

Clinical trials with chondroitin sulfate and glucosamine, used alone or in combination in people, revealed symptomatic relief similar to that of ibuprofen.[183] Unfortunately, most studies lack appropriate controls and are complicated by the co-administration of other medications.[184,185] Recommendations from recent meta-analyses, a type of study using stringent criteria for inclusion and statistical analyses of other published studies, call for additional trials with larger cohorts of patients studied for longer periods of time.[186,187] Interestingly, in military personnel with spinal and knee osteoarthritis, symptomatic relief was reported using a variety of subjective measures, but running times were unaffected by treatment.[188]

To date, clinical research in horses is limited,[189] and reported results vary from beneficial effects to limited value. Which horses will respond to oral supplementation is not known. Formulation of glucosamine and chondroitin sulfate–containing supplements is not regulated by the Food and Drug Administration (United States), so purity and content are not always ensured. Products with certified content from reputable sources should be used.

Common Practices in Medical Management

There are two principal objectives of medical management of the equine athlete: symptomatic relief and arresting progression of joint degeneration. As for people with rheumatic disease, no equine compound exists for which incontrovertible in vivo evidence of disease modification exists. Efficacy of most drugs is based subjectively on clinical experience. To assess trends in current practices of medical management of osteoarthritis, we sent questionnaires to 20 members of the American Association of Equine Practitioners for whom the treatment of performance horse lameness was particularly common. The survey included questions regarding the use and perceived efficacy of NSAIDs, corticosteroids, hyaluronan, PSGAG, and nutriceuticals (glucosamine and chondroitin sulfate–containing products). Fourteen responses were returned, including from five veterinarians working exclusively with Thoroughbred racehorses, two exclusively with Standardbred racehorses, four with Western or show horses (hunting, jumping, dressage, other show) or both, and three who treated racing and show breeds. Collectively, respondents treated an estimated 17,000 horses with osteoarthritis annually and most estimated that osteoarthritis accounted for at least 60% of their lameness case load.

Non-Steroidal Anti-Inflammatory Drugs

All respondents used NSAIDs and phenylbutazone was the most frequently used. Cited advantages included cost, efficacy, and anti-inflammatory potency compared with other compounds; ability to administer the drug by a variety of routes; and relative lack and predictability of toxic effects. NSAIDs were considered adjunctive and were seldom used alone.

Corticosteroids

All respondents but one used intra-articular injections of corticosteroids regularly (29%) or frequently (71%). Common indications for corticosteroid use included recurrent osteoarthritis in horses that had previously responded well to intra-articular medication and subacute or chronic osteoarthritis that was unresponsive to other therapies. Acute signs of osteoarthritis were managed less commonly with intra-articularly administered corticosteroids. Some clinicians combined corticosteroids with local anesthetic solutions when performing diagnostic analgesia. Corticosteroids were seldom used alone and in 50% of horses were used with intra-articularly administered hyaluronan.

Among the available products, methylprednisolone acetate was the most popular; it was used (although not exclusively) by 12 respondents. Among these veterinarians, eight opined that methylprednisolone acetate was more effective or had a greater duration of activity than other corticosteroid preparations. The second most popular preparation was triamcinolone acetonide. Dose varied among veterinarians and was also dependent on the volume of the synovial cavity being treated. About 50% of clinicians used methylprednisolone acetate and triamcinolone acetonide at relatively low doses (e.g., 40 mg and 6 mg per articulation, respectively), and the rest used higher doses (e.g., 100 to 120 mg and 12 to 18 mg per articulation, respectively). Intra-articularly administered corticosteroids were more popular and tended to be used at higher doses by racetrack clinicians than by those treating other sport horses. Overall, intra-articularly administered corticosteroids were considered effective for managing horses with acute synovitis and somewhat less so in those with established osteoarthritis (Fig. 85-2, *A*). Notably, estimates of efficacy were similar, regardless of whether low or high doses were used.

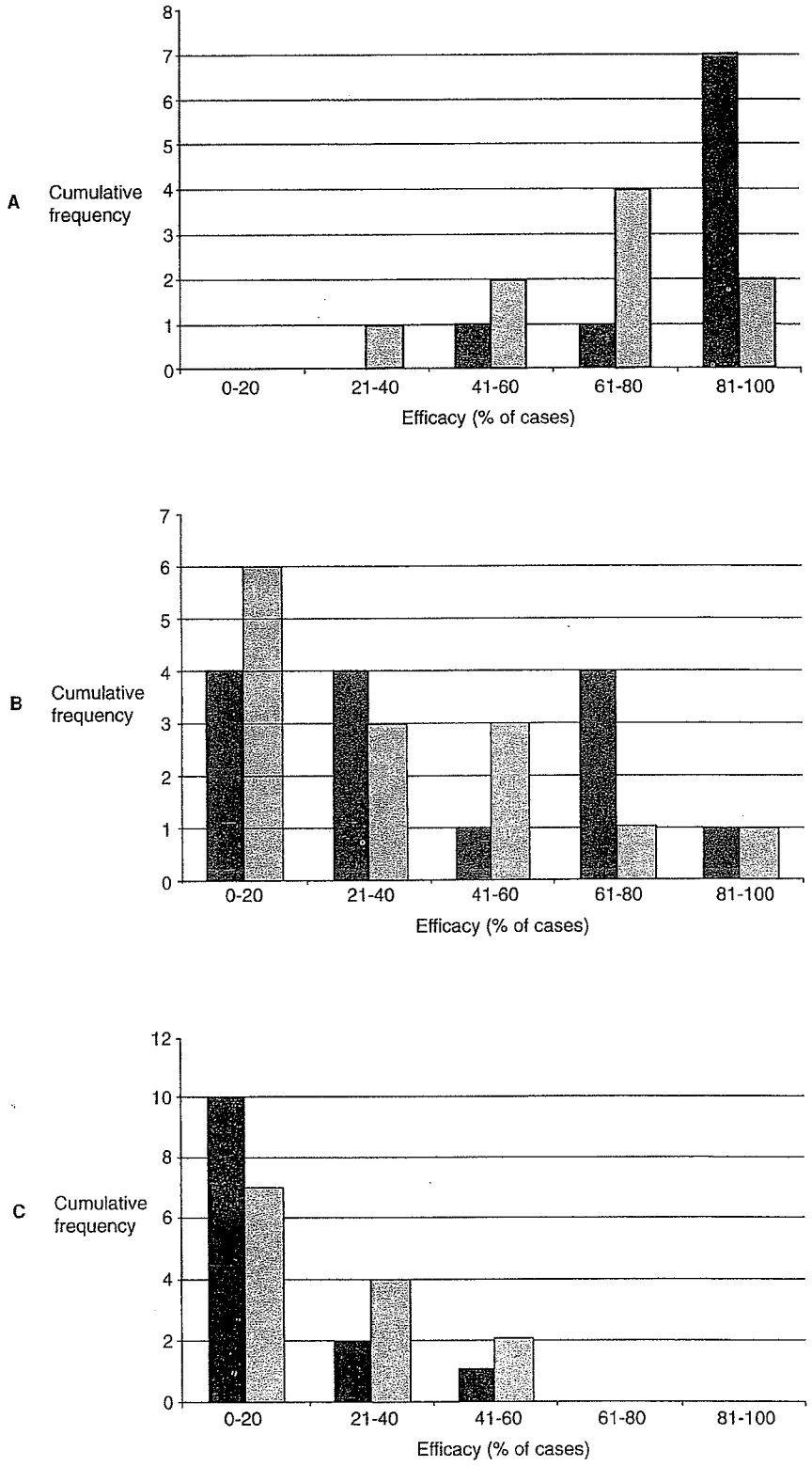

Fig. 85-2 Selected survey results to a joint disease medication survey of 14 members of the American Association of Equine Practitioners for whom the treatment of performance horse lameness was particularly common. The graphs represent the perceived efficacy of the symptomatic treatment of acute synovitis *(solid bars)* and established joint disease *(gray bars)* as follows: A, intra-articularly administered corticosteroids; B, intravenously administered hyaluronan; and C, orally administered glucosamine/chondroitin sulfate–containing nutriceutical products.

Hyaluronan

All respondents used intra-articularly administered hyaluronan, but for hyaluronan to be used initially or alone was uncommon, particularly in horses with established osteoarthritis. Twelve (86%) of 14 supplemented hyaluronan injections with other forms of treatment, most commonly concurrent administration of intra-articularly administered corticosteroids, particularly among those who treated Thoroughbred racehorses. Although combined use of corticosteroids and hyaluronan was also common among veterinarians treating show horses, two used hyaluronan alone 80% of the time.

Interestingly, seven clinicians chose to use hyaluronan preferentially in high-motion joints (e.g., middle carpal joint), whereas seven used the drug equally between high-motion and low-motion joints (e.g., centrodistal and tarsometatarsal joints). A variety of hyaluronan preparations were used and respondents were divided in their views on the relative efficacy of high and low molecular weight products. An unbiased evaluation of the therapeutic efficacy of intra-articularly administered hyaluronan was hampered by the co-administration of a corticosteroid preparation.

Most clinicians had experience treating horses with intravenous hyaluronan, but few, regardless of the type of horse treated, were impressed by its efficacy, particularly when used alone (Fig. 85-2, *B*). They opined that effects on osteoarthritis signs were not dramatic and duration was short.

Polysulfated Glycosaminoglycan

PSGAG use was common. Six of seven racehorse veterinarians used intra-articularly administered PSGAG at least occasionally, whereas a similar number of non-racehorse veterinarians avoided the practice. Intra-articularly administered PSGAG was used most commonly in horses with recurrent clinical signs or those with sub-acute or chronic conditions that were unresponsive to other therapy. Indications for intramuscular use varied widely. In addition to the indications listed for intra-articular administration, intramuscularly administered PSGAG was used to treat horses with acute or recurrent chronic osteoarthritis, or both types. PSGAG was also used as a preventative measure. PSGAGs were used with other treatments and estimates of efficacy were diverse, ranging from completely ineffective, to constituting a major element of therapy.

Glucosamine and Chondroitin Sulfate

Most respondents had experience with nutriceuticals, but unlike other compounds they were used most commonly as a preventative measure, often at the request of an owner or trainer. These products were considered substantially less effective than the other medications (Fig. 85-2, C). Most considered these products adjunctive at best, and no trend favored one product over another.

Overall, considerable variation existed regarding medical management of osteoarthritis, but certain themes emerged. Phenylbutazone remains the most popular NSAID, was effective, and often is used with intra-articular injections. Intra-articular injections of corticosteroid and hyaluronan, often in combination, are frequently used to manage acute and chronic osteoarthritis in all sport horses. Opinions were divided regarding the purported superiority of high molecular weight hyaluronan when injected intra-articularly, but the consensus was that intravenously administered hyaluronan was of limited value. PSGAG use remains popular, but considerable variation existed in the indications for use and perceived efficacy. Little support was given for the routine therapeutic use of nutriceuticals.

Intra-Articular Medications: Practical Considerations

Intra-articularly administered medications are important in managing osteoarthritis, yet no clear consensus is apparent regarding specific practices and precautions. Given the gravity of post-injection infection, in particular when resistant bacteria such as methicillin-resistant *Staphylococcus aureus* are involved, strict adherence to aseptic technique is mandatory. An appropriate standard includes thorough surgical preparation of the intended injection site and using sterile gloves and single-use syringes and needles. Multiple dose bottles or vials of any preparation intended for intra-articular use should be avoided. Although long accepted, the practice of clipping or shaving the injection site has been challenged recently by a study demonstrating that bacterial numbers were comparable between surgically prepared clipped and unclipped injection sites of the equine carpus and distal interphalangeal joints.[190]

No consensus exists on duration of rest after an intra-articular injection, largely from lack of objective information. Supported by various reports, recommendations vary from immediate resumption of exercise to 30 days of rest from training after any injection. Variation in recommendations is not unique to the equine practitioner. In a survey of the members of the American College of Rheumatology, recommendations for rest after intra-articular corticosteroid injections in people varied from 48 hours or less to 1 week or more.[191] Clearly the nature and severity of osteoarthritis should be considered. Because compelling evidence exists that corticosteroids have inhibitory effects on cartilage matrix metabolism, the dose of corticosteroid must be considered. Mechanical properties of cartilage in corticosteroid-treated joints are altered,[192] and although normal loading of cartilage has beneficial metabolic effects, heavy loading can compound the inhibitory effects of corticosteroid on matrix synthesis.[193] Unfortunately, most studies have used generous corticosteroid doses and normal cartilage that responds differently to osteoarthritic cartilage.[82-84,194] Nonetheless, the deleterious effects of exercise after intra-articular corticosteroid injections have been over-rated.[82,83] Moreover, industry pressures often militate against prolonged periods of rest after injections. After considering all factors, we recommend horses be given 2 to 3 days of box (stall) rest with hand walking, followed by a gradual return to light training, after intra-articular injections of corticosteroid. Similar recommendations are given for injections with hyaluronan and PSGAGs, even though issues such as inhibition of matrix synthesis are less important with these drugs.

Despite a near complete lack of knowledge of effects of mixing local anesthetic solutions with corticosteroids for intra-articular injections, rheumatologists commonly mix both in the same syringe to reduce pain, dilute corticosteroid suspensions, reduce post-injection flare, and help diagnose the source of pain.[191] Equine veterinarians often combine the two solutions to investigate and treat a source of pain simultaneously. Conversely, some clinicians avoid a second intra-articular injection if local anesthetic solution was injected recently. Local anesthetic agents cause a mild inflammatory response in joints,[195] but it is unclear whether inflammation or drug interactions influence the therapeutic response to concurrently or sequentially injected medications or substantially increase the risks of post-injection infection. We do not recommend routine use of combined injections.

Post-injection flare causes pronounced synovial effusion and often substantial lameness and usually occurs 4 to 24 hours after injection. Rapid response to lavage and anti-inflammatory therapy is usually seen. However, appropriate antimicrobial therapy should be instituted, and synovial fluid samples should be submitted for culture and susceptibility testing and cytological examination.

Medical Management: Conclusions

From objective and subjective information presented, clearly specific recommendations for all situations are difficult to make. Management choices are still made based on general principles, past experience, and economic considerations,

and the evolution of these regimens often is determined by therapeutic response. Given the complexity and variations of osteoarthritis and paucity of specific knowledge regarding the effects of available medications, veterinarians still must tailor treatments individually.

SURGICAL TREATMENT

Diagnostic and Surgical Arthroscopy

The application of arthroscopic techniques to the horse has revolutionized the treatment of traumatic joint injuries.[196,197] The advantages and disadvantages of arthroscopic surgery are discussed in Chapter 23, but importantly, arthroscopic surgery is the imaging modality of choice to evaluate articular cartilage (Fig. 85-3), although magnetic resonance imaging may supersede it in the future, particularly in joints with limited surgical access (see Chapter 21). Diagnostic arthroscopy is particularly useful in horses without radiographically visible lesions.[198]

Arthroscopic surgery is useful in surgical management of osteoarthritis. Since the advent of arthroscopic surgery, fractures of the proximal, dorsal aspect of the proximal phalanx are once again removed, with favorable results. The practice had previously been suspended when arthrotomy was performed, because low-grade lameness attributed to capsular fibrosis or calcification was often seen.[196,199] Intra-articular lavage is a benefit from arthroscopic surgery, because inflammatory debris and cartilage fragments are washed from the joint. Joint lavage is itself an important consideration in managing inflamed joints. In people with osteoarthritis, joint lavage alone is comparable to other forms of medical therapy. In Standardbreds in training, injection of small volumes of saline solution combined with 3 weeks' rest was more effective than rest alone in alleviating clinical signs of traumatic arthritis.[200-203]

Arthroscopic surgery is most useful in surgical management of osteoarthritis by eliminating the inciting cause and preventing the progression of osteoarthritis rather than treating established lesions. The most common indication for arthroscopic surgery is the removal of osteochondral fragments of traumatic or developmental origin. The ideal candidate is a horse that has not been injected previously with corticosteroids. Prognosis is favorable for horses after arthroscopic surgery to remove small osteochondral fragments, but before secondary changes of osteoarthritis have developed. However, osteochondral fragments often occur with, or result from, osteoarthritis (see Chapter 39) and this reduces the prognosis.[204,205] Presence of radiographic changes of osteoarthritis before surgery reduces prognosis in any horse with osteochondral fragments. In horses with advanced radiographic evidence of osteoarthritis, arthroscopic surgery may be useful to assess the magnitude of cartilage damage and to provide temporary symptomatic relief, but it is of dubious value in making a positive impact on long-term prognosis. In horses with established osteoarthritis, client education is important and horses may best be managed medically. Case selection is most important when considering arthroscopic surgery or arthrotomy for management of any articular problem (see Chapter 23).

Specific arthroscopic techniques are well established and detailed descriptions are available.[196] Controversy lingers regarding the vigor with which debridement of articular tissues should be performed. Currently, minimal effective debridement is advocated because articular cartilage has limited capacity for intrinsic repair.[197] Conversely, diseased bone should be completely removed.

Care after surgery involves the principles of providing an environment for resolution of inflammation, providing stability and restricting joint motion to facilitate optimal healing of articular tissues, and preventing post-operative contamination. Rest is important to reduce articular trauma and to minimize disruption of fragile repair tissues. NSAIDs are administered for 3 to 5 days to reduce inflammation from surgical trauma. Appropriate bandaging and rehabilitation are important (see Chapters 87 and 92). Although popular, the intra-articular use of hyaluronan and PSGAG after surgery had no beneficial effects on healing experimental cartilage defects.[206,207] Prognosis depends on several factors, but most importantly the magnitude and location of cartilage damage should be considered. For example, horses with carpal osteochondral fragments with 50% or more cartilage or subchondral bone loss have a significantly inferior prognosis than those with less severe lesions.[208]

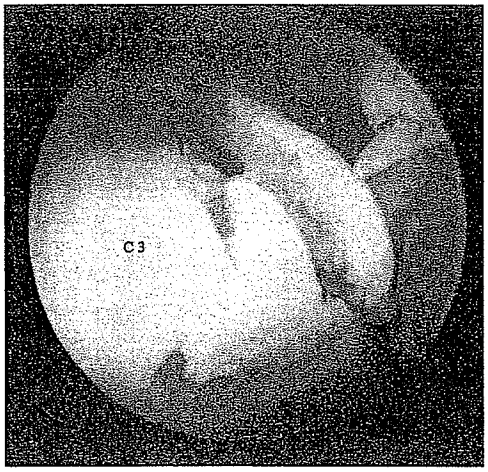

Fig. 85-3 Arthroscopic view (proximal is to the bottom) of the middle carpal joint in Standardbred racehorse with sizeable osteochondral fragments from the third carpal bone (C3). Beyond removal of osteochondral fractures, arthroscopic examination allowed determination of the magnitude of cartilage damage extending onto the weight-bearing surface of the third carpal bone and assessment of the degree of cartilage damage to the opposing surface of the radial carpal bone.

Internal Fixation of Intra-Articular Fractures

Common intra-articular fractures managed by lag screw techniques include third carpal bone slab fractures, lateral (and medial) third metacarpal/metatarsal bone condylar fractures, and sagittal fractures of the proximal phalanx. Internal fixation of displaced, intra-articular fractures involving sizable portions of the articular surfaces of these and other bones offers the greatest possibility for the horses to return to function. Repair of non-displaced fractures may improve healing time and substantially reduced risk of delayed displacement of fracture fragments. In addition, experimental evidence suggests that cartilage healing is superior with stable internal fixation of intra-articular fractures.[209]

Internal fixation can and should be combined with diagnostic arthroscopy. Arthroscopic surgery can be useful to assess cartilage damage, facilitate the identification and removal of small osteochondral fragments and debris in the fracture line, assess for comminution,[210] and evaluate reduction before implants are placed. The size and number of implants is dictated by fracture configuration and surgeon preference, and cortical bone screws are placed according to principles of the Association for the Study of Internal Fixation.[211,212] Appropriate positioning of implants to optimize reduction and congruity of articular components is facilitated by intra-operative radiography or fluoroscopy.

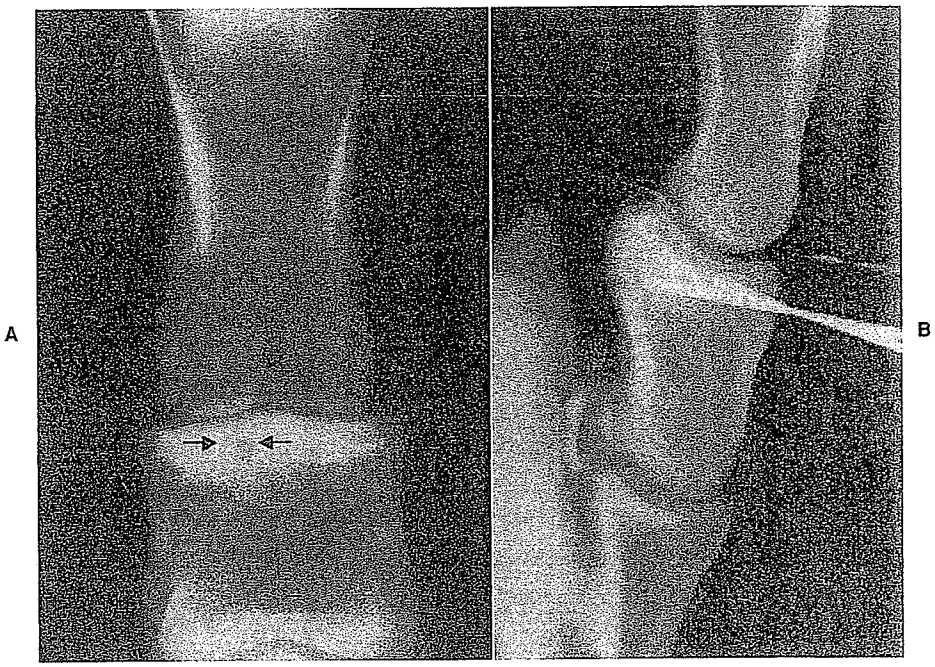

Fig. 85-4 A, Dorsopalmar and B, lateromedial radiographic views of the distal limb of a yearling with lameness referable to the proximal interphalangeal joint. A, There is an osseous cyst-like lesion (*arrows*) in the proximal aspect of the middle phalanx. B, The area was decompressed using transcortical drilling, and the procedure successfully abolished lameness.

Osseous Decompression

On occasion, joint pain may be referable to lesions of subchondral and epiphyseal bone that are not accessible arthroscopically. For example, subchondral cysts or osseous cyst-like lesions lacking a direct articular communication may occur under weight-bearing surfaces. Transcortical decompression has been successful in reducing lameness (Fig. 85-4). This empirical treatment is based on the principles of debridement of malacic bone and on the physiological premise that elevated metaphyseal pressures contribute to articular pain.

Synovectomy

Synovial resection, or synovectomy, involves removing inflamed, hypertrophic, or infected synovial membrane and can be accomplished surgically, with chemical agents, or using radioactive isotopes.[213] Synovial resection can be local (partial synovectomy) or generalized (subtotal or complete synovectomy).

In people with rheumatoid arthritis, early synovectomy provides temporary pain relief and reduces synovial inflammation. Symptomatic relief is typically more long-lasting for patients treated early in the course of the disease.[214,215] The rationale for the use of synovectomy in rheumatoid arthritis is intuitively clear, because the synovium has a well-established role in the disorder. In osteoarthritis the synovium plays a minor role in the disease process, and only mild response is observed in people with osteoarthritis treated by synovectomy.[216]

Specific indications and potential benefits of synovectomy in equine joint surgery have yet to be determined. Regeneration of the equine synovium after arthroscopically assisted synovectomy is slow compared with other species, but the procedure has negligible ill effects.[217-220] Arthroscopic synovectomy is considered beneficial in reducing bacterial load and attenuating profound synovitis in chronically infected equine joints.[221] Results of synovectomy in managing horses with chronic, unresponsive infectious arthritis of the tarsocrural joint are favorable (Fig. 85-5).

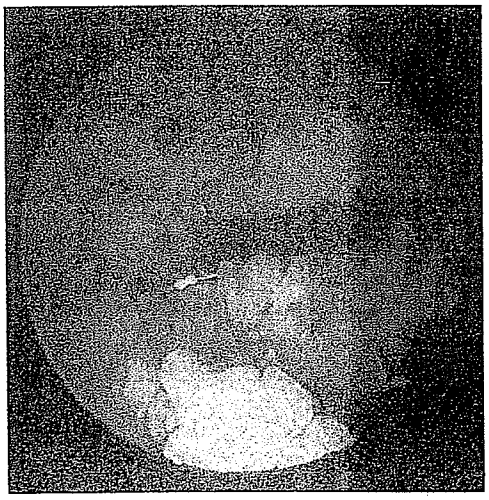

Fig. 85-5 Arthroscopic view of the tarsocrural joint of a racehorse with chronic active synovitis that was refractory to medical treatment. Greatly enlarged and club-like synovial fronds (under the stainless steel elevator) are evident. The gelding responded favorably to subtotal synovectomy.

To date, no compelling evidence supports the routine use of subtotal synovectomy in treating horses with osteoarthritis. Synovectomy was reported to be effective in reducing lameness from chronic proliferative synovitis of the fetlock and carpal joints of racehorses.[222]

Arthrodesis

In some horses, osteoarthritis is severe and cannot be managed medically or by conventional surgical techniques. Often concern

exists about laminitis of the contralateral limb and euthanasia may be considered if the horse has no residual value as a breeding prospect. In horses with chronic, severe, and refractory osteoarthritis of low-motion joints, such as the proximal interphalangeal and distal tarsal joints, arthrodesis can preserve athletic function.[223-227] Arthrodesis can be performed using internal fixation and external coaptation or by using chemical means.[228,229] Arthrodesis of high-motion joints, including the scapulohumeral, antebrachiocarpal or middle carpal, metacarpophalangeal, and distal interphalangeal joints, is performed as a salvage procedure.[230-233]

INVESTIGATIONAL TREATMENTS

Experimental treatments used in people may be applicable to horses. Active areas of research include cartilage resurfacing and limiting the effects of known biological mediators of osteoarthritis. Preliminary results using these approaches, alone or in combination, have been encouraging, though a number of biological and technical obstacles remain.

Joint Resurfacing

Cartilage loss is one hallmark of osteoarthritis. Cartilage has limited capacity for repair and considerable effort has been expended in attempts to augment intrinsic healing or to replace it. A number of approaches currently are being explored to provide a biochemically and biomechanically suitable repair tissue for equine osteochondral defects.

The healing of partial thickness cartilage defects is ineffectual, and the recruitment of a larger population of cells than that which exists in the adjacent matrix is required for optimal healing to occur. Attempts to improve the natural healing process typically involve debridement of the subchondral plate, or other methods to recruit pluripotent cells from the marrow cavity (stimulated endogenous repair), or the delivery of chondrogenic tissues, chondrocytes, or pluripotential cells to the defect (articular grafting). To date, the long-term efforts to modulate healing of cartilage defects have been disappointing, because formation of true hyaline cartilage has not occurred.[234-236] The biochemical composition of repair tissues frequently lacks appropriate macromolecules, specifically type II collagen, and a normal concentration of proteoglycans of suitable size and structure. Lacking the required composition, the biomechanical performance of the tissue is less than ideal and ultimately leads to its breakdown.

Stimulated Endogenous Repair

Stimulating endogenous repair in equine joints involves techniques to provide access of marrow elements to the cartilage defect (e.g., subchondral drilling), but results have not paralleled those in laboratory species. Problems of dedifferentiation of the repair tissue to a largely fibrous tissue composition have occurred. This fibrous tissue lacks the required functional characteristics.[237,238]

More recently, a technique involving the creation of microfractures in the subchondral plate to allow access of marrow pluripotential cells to the cartilage defect was developed. Known as *micropicking* or *breaching*, a stainless steel awl is used to create small crack-like defects in the articular end plate, usually under arthroscopic control.[239,240] Micropicking is a simple and atraumatic way to provide pluripotent cells, and proponents cite the lack of heat generated as one reason that results are superior to drilling techniques.[241] Another advantage of micropicking is that it preserves the subchondral plate. This is noteworthy because destruction of the subchondral plate typically compromises any resurfacing effort.[234] Experimental use of micropicking in normal horses resulted in more voluminous repair tissue than controls; however, little difference in repair tissue quality was apparent.[242] Although reports of using micropicking to treat traumatic injuries in human athletes are encouraging, the indications and long-term results of the procedure in the horse are unknown.

Articular Grafting

Initially, studies using onlay grafts of periosteum or perichondrium for resurfacing of cartilage defects in laboratory animals generated much excitement. Attempts to apply this approach in the horse were disappointing and research efforts have shifted focus to grafts of cultured chondrocytes or cartilage-progenitor cells contained in an appropriate substrate.[235,243,244] To date, uniformly successful results have not been achieved using these methods. The problems of graft incorporation, cell survival, and an inability to maintain a functional hyaline cartilage repair persist. Recent studies are beginning to shed more light on the specific idiosyncrasies of cell metabolism in cartilage defects, and soon improving repair tissue quality through more precise regulation of cell metabolism in the various strata of the healing wound may be possible.[245-247]

Biologically Based Therapies

Biological therapy is intended to modulate the extent of immunological or inflammatory events while maintaining appropriate tissue function and responses. The goal of this approach is to control the excessive activation of the various mediators leading to cartilage degradation. Inhibition can be accomplished directly or indirectly. Areas of active investigation include administering MMP blockers, drugs that directly inhibit inflammatory cytokines (e.g., interleukin-1), and providing natural inhibitors of proteinases or cytokines. For example, efforts at suppressing cartilage matrix degradation have been conducted using natural[248,249] or synthetic matrix MMP inhibitors.[248,250,251] Another strategy to prevent proteolytic cartilage degradation is to inhibit the synthesis or activity of mediators responsible for stimulating the synthesis enzymes. For example, matrix MMP release is stimulated by interleukin-1, a process that can be blocked by interleukin-1 receptor antagonist protein, a naturally occurring inhibitor of interleukin-1. Intra-articular administration of interleukin-1 receptor antagonist protein slows the progression of lesions in experimental osteoarthritis.[252,253] Similarly, antibodies and soluble receptors to tumor necrosis factor-α, another pro-inflammatory cytokine implicated in arthritis, reduced cartilage loss in collagen-induced arthritis in mice.[254,255] In addition to specific inhibitors, treatment with proteins that indirectly block the effects of inflammatory mediators may be of therapeutic value. An example includes administering interleukin-4, a blocking cytokine with metabolic effects opposite to those of recognized pro-inflammatory forms, such as interleukin-1 or tumor necrosis factor-α.[256] Another approach is to attempt to enhance matrix synthesis and repair. This method involves administering cytokines such as basic fibroblast growth factor or insulin-like growth factor, which have been shown to influence cartilage metabolism and healing favorably.[257,258]

Unfortunately, the actions of many of these therapeutic proteins are short-lived, which necessitates frequent administration. Gene therapy represents a potential means by which delivery of some of the mentioned therapeutic proteins may be possible.[259,260] Although technical aspects of the approach vary, the general principle involves introducing a gene that enables cells within the joint to synthesize one or more therapeutic product(s) (Fig. 85-6). Genes coding for anti-arthritic proteins are the most obvious choice, but bioactive ribonucleic acid (RNA) molecules or antisense RNA could also be valuable. The advantage of gene therapy is that, once the gene is present, theoretically the gene could be transcribed and translated many millions of times to produce a therapeutic level of its product. Candidate proteins for gene therapy include natural MMP inhibitors (e.g., tissue inhibitors of metalloproteinases), cytokines (e.g., insulin-like growth factor), and cytokine

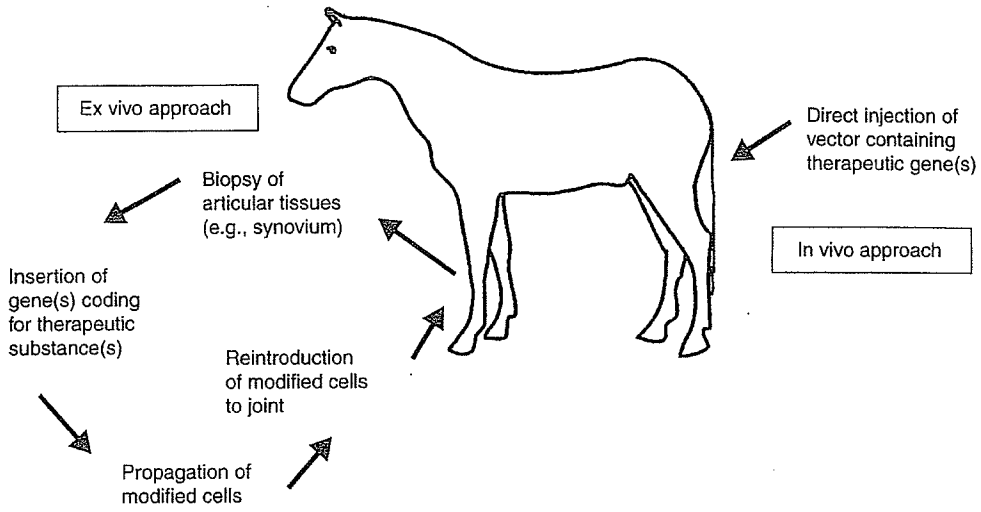

Fig. 85-6 General approaches for equine joint disease using local gene therapy. A vector containing one or more therapeutic genes can be injected directly into the affected joint (in vivo approach), or a biopsy containing patient cells may be transfected with a vector (frequently viral) containing the genes of interest, after which the cells are propagated in culture and re-introduced to the joint in large numbers (ex vivo approach).

inhibitors (e.g., interleukin-1 receptor antagonist protein). Inhibition of cartilage degradation has occupied much of the research efforts to date, many involving experiments designed to block the effects of interleukin-1 on cartilage degradation.[261,262] The interleukin-1 receptor antagonist gene was introduced successfully into normal equine joints, and preliminary results in an experimental joint disease model were favorable.[263,264] Promoting matrix synthesis is another potential application of gene therapy. For example, transfer of growth factor constructs (transforming growth factor-β1, insulin-like growth factor 1, and bone morphogenic protein 2) to chondrocytes was successful in increasing synthesis of collagen and proteoglycan.[265,266]

Durable resurfacing of cartilage defects ultimately may be accomplished with a combination of chondroprogenitor cell transplantation and gene therapy, with the introduction of genes coding for one or more selected growth factors. Theoretically, if the correct combination of proteins could be expressed in appropriate quantities, at the correct times during healing and incorporation of the transplanted cells, modulation of grafted or endogenous repair tissues to hyaline cartilage may well be possible.

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CHAPTER • 86

Epidural Analgesia and Hindlimb Lameness

Rose M. McMurphy

The benefits of providing analgesia for acute and chronic pain have been well established in many species. Inadequate treatment of pain in animals can result in inappetence and weight loss, increases in serum cortisol and catecholamines, tachycardia, hypertension, and compromise of the immune system.[1] Increases in serum cortisol and catecholamines can cause derangements in serum glucose, protein metabolism, and immune function. In addition, horses with a painful limb may remain recumbent for prolonged periods of time, with resultant decubital ulcer formation and secondary infection.

Designing an appropriate plan for analgesia in horses, particularly for those with severe, chronic pain can be challenging. Parenterally administered opioids and α_2-adrenergic agonists may be associated with side effects such as ataxia and excitement, and adverse effects on the gastrointestinal and cardiovascular systems. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause gastrointestinal ulceration or renal disease, and they may be inadequate for horses with acute, intense pain. Epidural administration of drugs provides a more localized analgesia and fewer systemic effects than parenteral administration.

Epidural drug administration places a drug in close proximity to its site of action within the spinal cord or spinal nerves as they exit the spinal cord. A greater analgesic effect may be achieved with a smaller total dose of a drug. The duration of analgesia is usually longer than with parenteral administration.

SCRIP Reports

INNOVATION IN ARTHRITIS TREATMENT:

A market revolution

By

Rosemary C Bonney PhD

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CONTENTS

EXECUTIVE SUMMARY

A revolution is taking place in the treatment of arthritis. After 10 years when no new types of arthritis drug were launched, some breakthrough products have at last reached worldwide markets. This is the culmination of intense investment in arthritis R&D by the pharmaceutical industry. Two major factors which prompted this investment were the dramatic growth which this already large market is experiencing and the continuing unmet medical need for effective arthritis therapies.

The two major types of arthritis are osteoarthritis and rheumatoid arthritis. They are chronic debilitating diseases with high prevalence, particularly among the elderly. Their prevalence is increasing rapidly as the world's population balance changes and more people get older. As a result, the market for arthritis treatments has grown and will continue to grow.

Treatment options have for a long time been far from ideal. Whilst drugs could alleviate some painful symptoms of arthritis, adverse events were widespread and many treatments lost their effectiveness during chronic use. The new drugs are not cures, but they act much more specifically than older products, meaning greatly improved efficacy and fewer adverse events.

Two of the new drugs are non-steroidal anti-inflammatory drugs (NSAIDs) which selectively inhibit the enzyme cyclooxygenase-2 (COX-2). NSAIDs have for a long time been used to reduce inflammation, relieve pain and improve joint function in arthritis, but they can cause serious gastrointestinal adverse events. The old NSAIDs inhibited both COX-2 and another COX isoform, COX-1. We now know that while COX-2 is involved in inflammation, COX-1 is associated with normal gastrointestinal events. By affecting only COX-2, the new selective products are expected to offer greater safety if not improved efficacy over existing NSAIDs. The first of these new drugs is Searle's celecoxib (Celebrex), which is 400-fold more selective for COX-2 than COX-1. It was launched in the US for the treatment of osteoarthritis and rheumatoid arthritis in January 1999 and has already achieved record prescription sales. Its rival is Merck & Co's rofecoxib (Vioxx), which has been approved in Mexico and the US. In addition to osteoarthritis, it is indicated for acute pain management, which could give it a competitive edge over celecoxib. Medical specialists and financial analysts predict that the sales of these drugs will reach more than $1 billion each and possibly up to $5 billion combined.

At the end of 1998, a new drug specifically for rheumatoid arthritis was launched in the US. Leflunomide (Arava) from Hoechst Marion Roussel is a disease-modifying antirheumatic drug (DMARD). It was the first DMARD to be approved for over a decade and the first to be indicated for delaying structural damage in rheumatoid arthritis. The description DMARD is used for a disparate group of drugs which slow joint destruction and reduce disability. A range of problems are associated with their use, including renal and hepatic toxicity, delayed onset of action (4–12 weeks) and loss of effectiveness because of prolonged use. Leflunomide acts selectively on lymphocytes, preventing their damaging autoimmune effects. Whether its selective activity offers improved efficacy and safety is a subject for discussion.

A further new group of drugs has been designed to target the inflammatory mediator tumour necrosis factor-α (TNF-α), which was discovered through research into the inflammatory processes of rheumatoid arthritis. Its central role made it an attractive therapeutic target for developing anti-arthritis drugs. Etanercept (Immunex's Enbrel) is a TNF-α receptor p75 fusion protein which competitively inhibits the binding of TNF-α to the TNF-α receptor,

thereby inhibiting the activity of TNF-α. It has been launched for the treatment of rheumatoid arthritis and promises to contribute a novel alternative treatment to the current DMARDs, possibly replacing them in the future. In contrast, infliximab (Centocor's Remicade) and D2E7 (Knoll) are monoclonal antibodies which specifically target TNF-α. All three drugs represent a major advance in the management of rheumatoid arthritis, but are not totally without side effects. Their full potential has yet to be demonstrated, particularly with respect to disease progression.

A number of companies are investigating other novel approaches to the treatment of arthritis. The report highlights some of these and provides a comprehensive tabulated summary of all the arthritis drugs in clinical and preclinical development.

The report contains 17 company profiles representing a cross section of the companies marketing and developing arthritis therapies. It provides information on their background, financial highlights and arthritis drug development.

CHAPTER 2
AN OVERVIEW OF ARTHRITIS

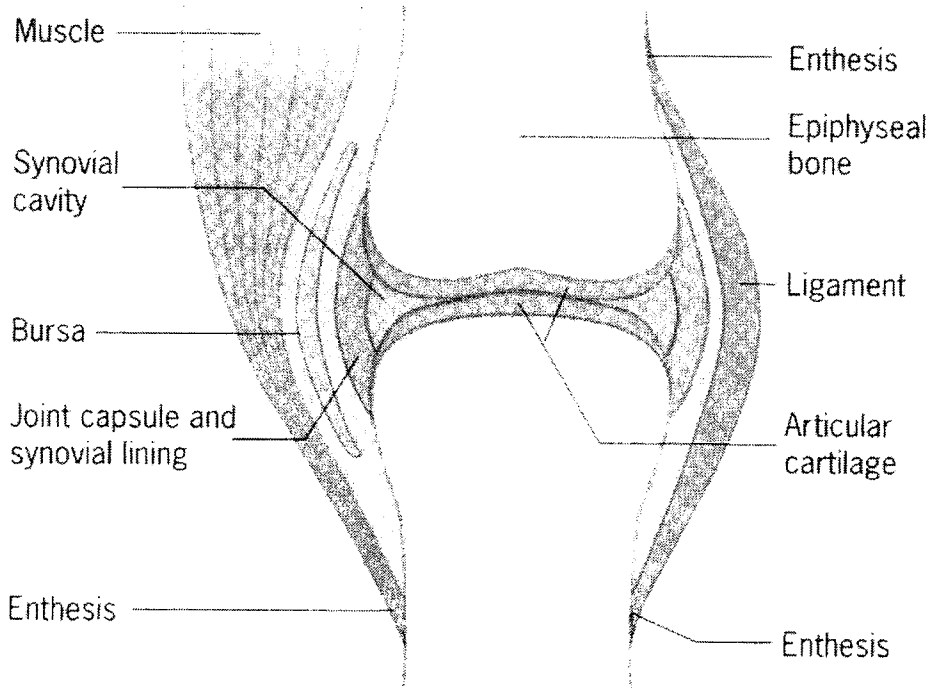
2.1 Arthritis defined

The word arthritis means literally 'inflammation of a joint' but it is often used in a broad sense to encompass the more than a hundred so-called rheumatic diseases (Arthritis Today, 1997). Such diseases affect not only the joints but also other connective tissues (muscles, tendons, ligaments and protective coverings of internal organs). The two major arthritis diseases, osteoarthritis and rheumatoid arthritis are discussed in depth below. Other common types of arthritis include ankylosing spondylitis (an inflammatory disease that affects the joints of the lower back which may lead to fusion of the spine) and gout (caused by the formation of uric acid crystals in the joint, leading to inflammation swelling and severe pain). These conditions will be discussed briefly later in this chapter.

2.2 The normal joint

In a normal mobile joint, (see Figure 2.1) the bone ends are covered with a protective layer of cartilage. The two cartilage surfaces never make contact because the synovial fluid lies between them, acting as a lubricant to facilitate the movement of the joint. The space filled with synovial fluid is known as the synovial or joint cavity. It is defined by the joint capsule, a protective envelope which consists of a thin layer of synovial cells (the synovium) embedded in a well vascularised extracellular matrix. The joint capsule is eventually stabilised by the ligaments of the joint.

Figure 2.1: The normal joint



Source: Kumar P J and Clark M L (Eds). Clinical Medicine, Fourth Edition, 1998. W B Saunders: London. Published with permission.

The normal synovial membrane is a few cells thick and vascular. The surface layer is composed of macrophages and fibroblast-like cells. Synovial fluid is a highly viscous fluid secreted by the synovial cells.

Normal human articular cartilage is completely avascular. It is composed of chondrocytes surrounded by an extracellular matrix of collagen fibres which contain proteoglycan molecules. These proteoglycan molecules attract water which generates a positive pressure within the joint. Turnover of matrix molecules involves degrading enzymes, for example, matrix metalloproteinases (MMPs) whose activity is, in part, controlled by enzyme inhibitors (tissue inhibitors of MMPs). The integrity of the cartilage is dependent upon these local anabolic and catabolic actions and also on the action of cytokines. The interaction of cell membrane-associated adhesion molecules with the extracellular matrix is also a pivotal component of the process.

2.3 Osteoarthritis

Osteoarthritis is a non-inflammatory degenerative joint disease characterised by a splitting and fragmentation of the articular cartilage, hypertrophy of the bone and changes in the synovial membrane. These degenerative changes are accompanied by pain and stiffness and loss of function. The disease most commonly involves the neck, lower back, knees, hips and joints of the fingers. It is the most common type of arthritis, occurring in about 10% of the population overall and affecting 50% of those over the age of 60 (Kumar & Clark, 1990). In developed countries osteoarthritis is the major reason for hip and knee replacements and as a cause of invalidity, it is surpassed only by the coronary diseases (Hamerman, 1989).

Osteoarthritis can also develop in joints that have suffered injury in the past or have been subjected to prolonged heavy use.

2.3.1 Aetiology and pathogenesis

The initiation and progression of osteoarthritis involves multiple pathogenic mechanisms. Its aetiology is essentially unknown.

The disease is characterised by progressive degradation of the components of the extracellular matrix of the articular cartilage, associated with secondary inflammatory factors. It differs from rheumatoid arthritis in that it is primarily a degeneration of the joint tissue which may be accompanied by an inflammatory reaction. Rheumatoid arthritis, on the other hand, is an inflammatory disease first and foremost and inflammation of the synovium is the focal point of the disease.

Cartilage destruction is thought to arise from an imbalance between chondrocyte-controlled anabolic and catabolic processes. The chondrocyte is believed to initiate the deterioration of the joint by releasing collagenases, enzymes that degrade collagen and proteoglycans. Damage to the collagen fibres permits the uptake of water which makes the cartilage swell and split. Crystals are also released into the joint which cause synovial inflammation and may exacerbate the destruction of the cartilage. An attempt by the body to repair the situation leads to remodelling of the bone and produces the osteophytes which are characteristic of the disease process.

Osteoarthritis affects all components of the joint, including bone, muscles, tendons, fibrous capsule, synovial membrane and articular cartilage.

The pathogenesis of the disease has been classified into four stages (see Cicuttini & Spector, 1998). These are as follows:

- Initial repair: This is characterised by proliferation of chondrocytes and increased synthesis of extracellular matrix components and DNA

- Early-stage osteoarthritis: During the early stage of development, the synthesis and activity of protease enzymes is increased. This leads to excessive degradation of the extracellular matrix components and net degradation and loss of articular cartilage. There is focal swelling of the articular cartilage followed by the appearance of irregularities in its surface. The synthesis of extracellular matrix components and DNA is increased as is the synthesis and release of proteolytic enzymes. The synthesis of protease inhibitors may be decreased

- Intermediate-stage osteoarthritis: The components of the extracellular matrix are no longer synthesised but protease synthesis and activity remains elevated. This leads to progressive degradation and loss of articular cartilage. This stage is also characterised by the fibrillation (vertical splitting), detachment (horizontal splitting) and thinning of the cartilage

- Late-stage osteoarthritis: At this stage, several extracellular matrix components (water, proteoglycans and collagen) are further reduced and the synthesis and activity of proteases remains high until the articular cartilage is almost completely destroyed. Bony outgrowths, known as osteophytes, occur at the joint margins resulting in what is known as residual arthritis. Clinically, this stage is characterised by pain and limitation of joint movement

The disease is additive, moving slowly from joint to joint and progressing very slowly within individual joints. It has the greatest impact on weight-bearing joints such as the hips and knees. Involvement of these joints is the commonest cause of disability among the elderly.

2.3.2 Sites affected by osteoarthritis

The hand is a common site of peripheral joint involvement. Bony swellings occur in the fingers, at the distal interphalangeal joints (Heberden's nodes) and at the proximal interphalangeal joints (Bouchard's nodes). Initially the joints are inflamed but later the inflammation disappears leaving knobbly, often painless swellings. Osteoarthritis at this site has less impact on the overall disability of the patient but, nevertheless, it may have considerable limitations in situations where manual dexterity is important.

Hip disease is the most common reason for total hip replacement operations. Farmers and labourers have an increased risk of developing hip arthritis because of occupational influences (regular lifting).

The prevalence of osteoarthritis of the knee is 40% in individuals over the age of 75 years (Cicuttini & Spector, 1998). It is more common in women than in men and there is a strong relationship with obesity (obese individuals being generally more susceptible). Injury and occupational knee-bending and physical labour all contribute to the risk of developing the disease.

The term generalised arthritis describes the involvement of at least three joints or a group of joints. In women osteoarthritis is often more severe and more sudden in onset than other forms of the disease.

2.3.3 Epidemiology and risk factors

A number of factors increase the risk for the development of primary osteoarthritis. These are as follows:

- Age (the disease tends to start at around the age of 50 years)
- Genetics (there is a strong familial tendency)
- Gender (women have a greater predisposition than men)
- Obesity (especially regarding arthritis of the knees)
- Mechanical defects (for instance, damage to the joint)
- Biochemical defects (certain processes can initiate cartilage degeneration)

2.3.3.1 Age and gender

The prevalence of osteoarthritis in women in the age groups under 45 years, 45–60 years and over 65 years is 2%, 30% and 68% respectively. In men, the prevalence in the same age groups is 3%, 24.5% and 58% respectively (Cicuttini & Spector, 1998).

Below the age of 45 years, osteoarthritis (usually involving one or two joints) is more common in men but over the age of 55 years it is more common in women. In women in this age group it usually involves the knees, the first metacarpal and the interphalangeals. In the 55–74-year age group, osteoarthritis of the knee is more prevalent in women than in men (Cicuttini & Spector, 1998). The reasons for these gender differences are not known.

2.3.3.2 Race

Osteoporosis occurs in all populations irrespective of race, climate and geographical location. However, the disease can vary within different ethnic groups. For instance, hip disease is less common in Chinese and Asians than in individuals of Western origin (Cicuttini & Spector, 1998). Osteoarthritis is also less common in black populations but when it does occur, it is the knee joint which is affected (Kumar & Clark, 1990).

2.3.3.3 Genetic associations

Some kinds of osteoarthritis are thought to be hereditary, particularly among women. For instance, the common form which causes enlargement of the knuckles has been found to be associated with a specific genetic abnormality. This genetic defect is responsible for a change of a single amino acid which causes the cartilage to degenerate prematurely.

The clinical evidence for the inheritance of osteoarthritis is summarised by Cicuttini & Spector (1998) as follows:

- Heberden's nodes (bony swellings at the distal interphalangeal joints of the fingers) are three times more common in the sisters of affected women compared with the general population

- 20% of individuals with osteoarthritis have a family history

- First-degree relatives have a two-fold increased risk of generalised arthritis
- There is greater concordance in identical twins at a number of joint sites
- The inheritability of radiological knee and hand osteoarthritis is 39–65%

2.3.3.4 Obesity

Obesity as a risk factor for osteoarthritis is particularly related to osteoarthritis of the knees. The reported increased risk is two-fold to seven-fold for women in the top tertile of body mass index compared with women in the bottom tertile (Cicuttini & Spector, 1998). The proportion of osteoarthritis which can be attributed to obesity has been estimated to be 63% in the middle-aged and 25% in the elderly (Cicuttini & Spector, 1998).

Obesity is an important risk factor because it can be modified by paying attention to diet and exercise.

2.3.3.5 Physical stress

There is indirect evidence to support a relationship between lengthy and high-intensity weight bearing exercise and osteoarthritis of the knee and hip. There are a number of studies regarding exercise and the development of osteoarthritis among athletes but the data are conflicting (Cicuttini & Spector, 1998).

2.3.4 Clinical features

Osteoarthritis develops gradually with increasing evidence of joint pain, stiffness, restricted movement and swelling of the joint. The swelling may be caused by synovitis (inflammation of the synovial membrane) with effusion or it may be caused by osteophyte formation (as in Heberden's nodes). This can result in joint deformity. In advanced disease, the articular cartilage is destroyed. Progression of the disease leads to a poorly functioning, painful joint.

Pain (usually in the knees, hips and hands) is worst in the evening, aggravated by use and relieved by rest. There is morning stiffness and stiffness after sitting. The degree of disability depends on the site involved. Pain and deformity of joints such as the knee and hip will immobilise the patient whereas similar changes in a hand joint will only affect their manual dexterity.

Little is known about the factors that influence the progression and regression of the disease.

2.3.5 Diagnosis and management

2.3.5.1 Diagnosis

Osteoarthritis is suspected when pain develops in the involved joints. It is confirmed by physical examination and X-rays and by excluding other types of arthritis. The most important change, as shown by X-ray, is the narrowing of the joint space due to loss of cartilage. It is accompanied by the formation of osteophytes at the margin of the joints, sclerosis of the underlying bone and cyst formation. In secondary osteoarthritis there is often calcification.

2.3.5.2 Management

The management of osteoarthritis comprises both pharmacological and non-pharmacological approaches. The aim is to relieve pain and to improve joint function.

. . . non-pharmacological treatment

Non-pharmacological therapy includes education, weight reduction, physiotherapy to restore joint movement and to increase the strength of the joint, application of heat and cold to relieve pain, ultrasound therapy, acupuncture, hydrotherapy and spa treatment. Joint surgery to repair or replace the joint (knee and hip disease) may be necessary.

. . . pharmacological treatment

Pharmacological therapy usually commences with simple analgesics and is followed by the use of NSAIDs, eg ibuprofen or naproxen sodium and may also include corticosteroid injections for acute relief.

NSAIDs are commonly used in osteoarthritis, despite their gastrointestinal side effects which include gastric irritation and ulceration, inhibition of platelet aggregation and prolonged bleeding time (discussed in Chapters 3 and 4). For this reason, paracetamol may be the preferred first-line analgesic. This is now likely to change with the introduction of the new COX-2 inhibitors (see Section 4.1).

Intra-articular therapy with corticosteroids is used in the treatment of osteoarthritis when, despite the use of other treatments, pain and swelling persist. They offer some short-term benefit.

2.4 Rheumatoid arthritis

Rheumatoid arthritis is a major crippling disorder and the most serious form of arthritis. It is a chronic, systemic, relapsing disease, primarily of the joints, which is marked by inflammatory changes in the synovial membranes and adjacent structures. Its characteristics include general ill health, chronic synovial inflammation of the joints (swelling or effusion), damage to the bone (erosions) inflammation of the tendons (tenosynovitis) and systemic disease. The fact that it is a systemic disease means that there are many extra-articular features associated with it.

The main symptoms are joint pain and stiffness. It commonly affects the small joints of the hands and feet but the larger joints may also be affected in time. The focal point of the disease is the synovial membrane.

2.4.1 Aetiology

Rheumatoid arthritis is of multifactorial aetiology although the exact cause is unknown. It appears to be due to a combination of environmental factors (eg infection) and genetic factors. Genes have, in fact, been identified that are responsible for more severe types of disease.

Other environmental factors that may influence the onset of the disease include lifestyle and hormonal status. The influence of the hormonal environment is demonstrated by the fact that remission occurs during pregnancy and the incidence of the disease in women is greater

before the menopause (Brooks, 1998). Oral contraceptives probably have no effect on the disease but may delay its onset.

2.4.2 Pathogenesis

Rheumatoid arthritis is considered to be an autoimmune disease (a condition in which the body's defence system mounts an immune reaction against itself) and its aetiology is similar to that of any autoimmune disease. When an immune cell (T or B lymphocyte) reacts to a self-protein during its development in the thymus or bone marrow the cell is usually killed or inactivated. Most T-cells never leave the thymus but undergo apoptosis *in situ*. However, occasionally a self-reactive cell (a T-cell or B-cell programmed to attack self-protein) escapes destruction and many years later can be activated to trigger an immune response. The trigger is thought to be infection with a bacterium or virus (retroviruses have been implicated) containing a protein with an amino acid sequence that matches a sequence in a tissue protein. The sequence need only be five amino acids long to induce an immune response. Bacteria which have been implicated in the aetiology of rheumatoid arthritis include *Streptococcus* spp, mycoplasmas and *Borrelia* spp (the agent of Lyme disease).

When the triggering agent enters the joint it causes an inflammatory reaction (see Chapter 1 for a general introduction). This involves damage to small blood vessels supplying the joint and the infiltration of macrophages, plasma cells and lymphocytes. Macrophages engulf the antigenic substances, process them and present them to the T lymphocytes. The T-cell requires a particular self-gene marker to respond to the antigen presenting cell and if it does not see it there is no reaction. The self gene marker is related to the HLA gene series. These are the MHC class II molecules and include HLA DR1 and HLA DR4, the latter molecule predicting a more severe type of rheumatoid arthritis. The antigen attaches to the MHC portion of the T-cell wall and activates the T-cells and macrophages. Activated T-cells produce cytokines which are mediators of inflammation.

Once the T-cell is triggered by the macrophage bearing the antigen particles on its surface, it stimulates the production of a cascade of cytokines and cytotoxins (prostaglandins, leukotrienes, free-radical oxygen). The cytokines send messages that recruit other cells into the area to mount an immune attack on the inflamed joint and they also activate these cells to perform specific tasks in the inflammatory response (Brennan *et al*, 1992) for example, the production of collagen destroying enzymes (collagenases). Other cytokines may promote the destruction of bone (Brennan *et al*, 1992; Elliott *et al*, 1995). The cytotoxins attack the tissue directly thus contributing to the overall disease effect.

The B-cells evolve into plasma cells. They produce antibodies that attack cells and target substances in the joint. As a result, the antibodies bind to their targets and form immune complexes which, in turn, trigger other immune cells to release complement proteins, some of which increase the permeability of blood vessels and allow more immune cells to enter. The B-cells also produce an abnormal antibody-related protein called rheumatoid factor which may or may not have diagnostic value (see below).

Other leukocytes are also involved in the inflammatory process in the joint. These include granulocytes, mononuclear cells, monocytes and macrophages. Monocytes and macrophages produce cytokines that contribute to the attack by releasing reactive oxygen species. They also produce copious quantities of collagenases and prostaglandins and/or proinflammatory cytokines (Burmester *et al*, 1997).

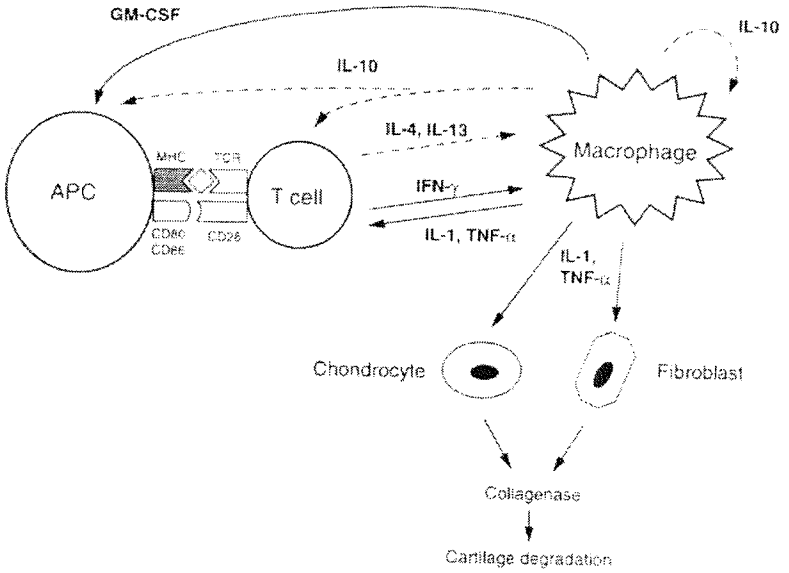
Large amounts of the proinflammatory (disease promoting) cytokines IL-1, TNF-α, IL-6 and GM-CSF are found in joints affected by rheumatoid arthritis. Similarly, significant amounts of anti-inflammatory (disease suppressing) cytokines and/or their soluble receptors are also present. These include IL-10, transforming growth factor-β (TGF-β), interleukin-1 receptor antagonist (IL-1ra) and soluble TNF-α receptors. However, these anti-inflammatory agents are unable to down-regulate the inflammatory process of rheumatoid arthritis thus supporting the concept that rheumatoid arthritis is the result of a cytokine imbalance (Jorgensen & Gay, 1998).

TNF-α is a macrophage-derived proinflammatory cytokine which is readily detected in both synovial fluid and synovial tissue (Isomäki & Punnonen, 1997). It is detected at the cartilage-pannus junction which suggests that it is involved in cartilage degradation (Chu *et al*, 1992). Soluble TNF-α receptors are also present in increased levels in the joints of patients with rheumatoid arthritis (Cope *et al*, 1992). They function as natural inhibitors of TNF-α by binding to it and preventing its attachment to cell surface receptors. Evidence for a pathogenic role for TNF-α in rheumatoid arthritis is afforded by the fact that TNF-α stimulates collagenase and PGE_2 production and induces cartilage and bone destruction in cell cultures (see Isomäki & Punnonen, 1997 for references and further information).

The proinflammatory cytokine IL-1 (which exists in two forms, IL-1α and IL-1β) and its natural antagonist IL-1ra are also present in the joints of patients with rheumatoid arthritis and are implicated in its pathogenesis. For instance, in cell cultures, IL-1 induces PGE and collagenase production by synovial cells and promotes bone resorption (see Isomäki & Punnonen, 1997 for references and relevant research).

A model of synovial inflammation in patients with rheumatoid arthritis is presented in Figure 2.2 .

Figure 2.2: A model of synovial inflammation in patients with rheumatoid arthritis

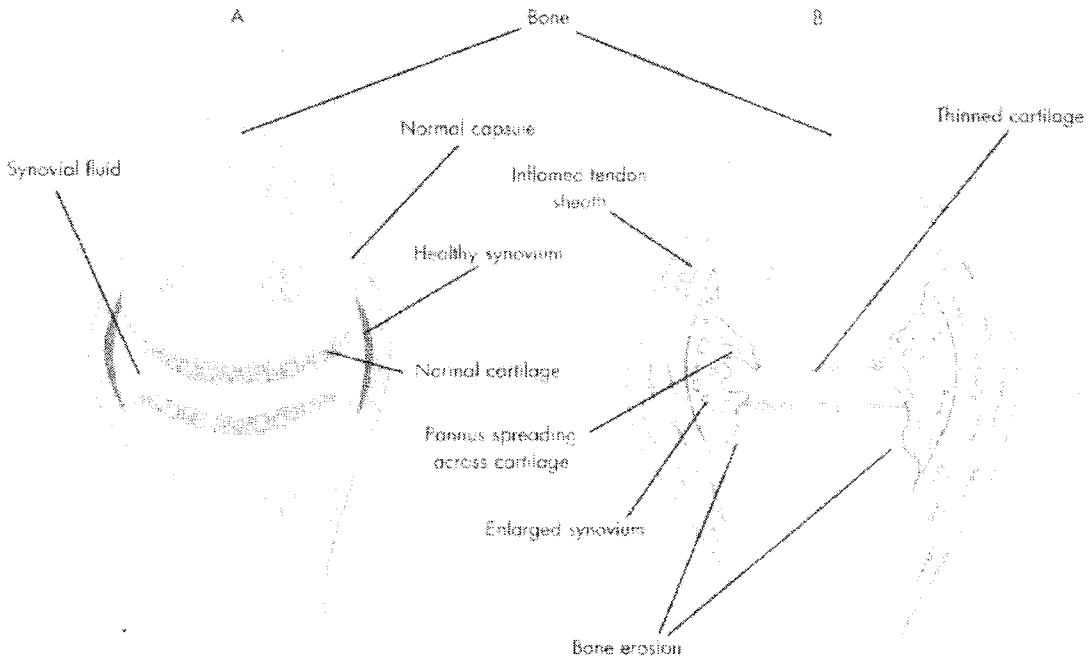


Source: Isomäki P and Punnonen J. Pro- and anti-inflammatory cytokines in rheumatoid arthritis. Annals of Medicine 1997; 29, 499 -507. Published with permission.

Concurrent with the initiation of the inflammatory reaction, the synovium responds to the ongoing attack by producing rapidly growing blood vessels. It proliferates and grows out over the surface of the cartilage to produce a tumour-like mass known as a pannus. This process causes the swollen, painful joints that are characteristic of rheumatoid arthritis. The pannus blocks the flow of tissue fluid that nourishes the cartilage. At the same time, granulocytes secrete enzymes that digest the cartilage and destroy it, leaving large areas of erosion.

Figure 2.3 shows a comparison between a healthy joint and one showing characteristics observed in rheumatoid arthritis.

Figure 2.3: A healthy joint (A) and one showing the characteristic changes observed in rheumatoid arthritis (B)



Source: Target Rheumatoid Arthritis, 1997.

2.4.3 Epidemiology

Rheumatoid arthritis is a common disease which affects 0.8–1.0% of adults. The prevalence is higher in women (the female:male ratio being 3:1) and is similar worldwide. The onset of the disease commonly occurs between the ages of 40 to 60 years although it can make its presence known at any age (see www.duq.edu/PT/rheumatoid arthritis/BackgroundOfTheDisease.html). In the US, there are an estimated 2.4 million cases and the annual incidence is reported to be 48 per 100,000 of the population (see www.aztec.co.za/users/drdoc/ra.html).

Brooks (1998) suggests that the incidence of the disease may be decreasing because, in the UK, the prevalence of rheumatoid arthritis in women aged 45–64 years decreased from 2.5% in 1958–1960 to 1.2% in 1990–1992. Similarly, the age-adjusted incidence among the Pima

Indians of south western US fell from almost 12 per 1,000 per year in 1966–1973 to 5 per 1,000 per year in 1983–1990.

Rheumatoid arthritis is an extremely disabling disease and carries a high mortality. Even with drug therapy, up to 7% of patients are disabled 5 years after the onset of the disease and 50% are too disabled to work after 10 years (see pharminfo.com/pubs/msb/rehumart.html).

2.4.4 Genetics

There is a familial component to rheumatoid arthritis and it often occurs in several members of the same family (5–10% of cases). There is an association with the HLA-DR4 gene in 70% of cases (Kumar & Clark, 1990). However, although this gene occurs in about 20–30% of the population, only 1% develops rheumatoid arthritis. This is because these inherited genes are susceptibility genes, that is, ones that make an individual more susceptible to the external trigger to the disease but do not indicate that the onset of the disease is inevitable (Target Rheumatoid Arthritis, 1997). It is also sporadic, there being no family history.

2.4.5 Clinical symptoms

Rheumatoid arthritis usually presents with the symptoms of pain and stiffness in the small joints of the hands and feet. In 25% of cases, a single joint, for example, the knee is affected at the time of presentation. In about 10% of cases the onset is sudden and severe (acute onset), in 20% the disease develops over a few weeks (sub-acute onset) and in 70% the symptoms develop slowly (insidious onset). Rheumatoid arthritis can affect all joints but is much more common in the hand and wrist (80–95% of people with the disease) while hip, jaw and elbow joints are affected in only 20–50% of cases (Target Rheumatoid Arthritis, 1997).

2.4.5.1 Diagnosis

The diagnosis of rheumatoid arthritis requires that a complete patient history should be taken and a physical examination should be carried out. The American College of Rheumatology (ACR) has specified seven clinical criteria and stipulates that at least four of them must be present for a diagnosis to be established. The first four criteria must have been present for at least 6 weeks.

- Morning stiffness lasting longer than 1 hour
- Soft tissue swelling in a hand joint
- Soft tissue swelling in at least three joint groups simultaneously (proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, metatarsophalangeal)
- Symmetrical swelling in one joint area
- The presence of rheumatoid nodules (swellings under the skin)
- Rheumatoid factor positive
- Radiographic evidence of changes to bone in the wrist or hands

The disease frequently presents in the metacarpophalangeal joints or the metatarsophalangeal joints and wrists and the joints are hot and swollen and tender to the touch. Morning stiffness is a common sign.

The clinical diagnosis is supported by blood tests and X-rays. The major blood tests used are the erythrocyte sedimentation rate (ESR) and C-reactive protein. These tests are general markers of inflammation or infection and not specific to rheumatoid arthritis. If they are raised, coincident with the appearance of inflamed and swollen joints, then rheumatoid arthritis is the likely explanation. An X-ray may not be useful in the early stages but, nevertheless, up to 30% of patients will have erosions suggestive of rheumatoid arthritis at the start.

The rheumatoid factor test can confirm the diagnosis in some instances but can be misleading. Rheumatoid factors are antibodies to the Fc portion human immunoglobulin which are found in 75–85% of rheumatoid arthritis patients but also in 1–5% of the general population. They are therefore not fundamental to the diagnosis. However, a high rheumatoid factor is a marker of more aggressive disease (see www.aztec.co.za/users/drdoc/ra.html) and is a more valuable diagnostic factor if it is high in a young person.

2.4.6 Stages in the development of rheumatoid arthritis

The development of the disease can be divided into three overlapping stages:

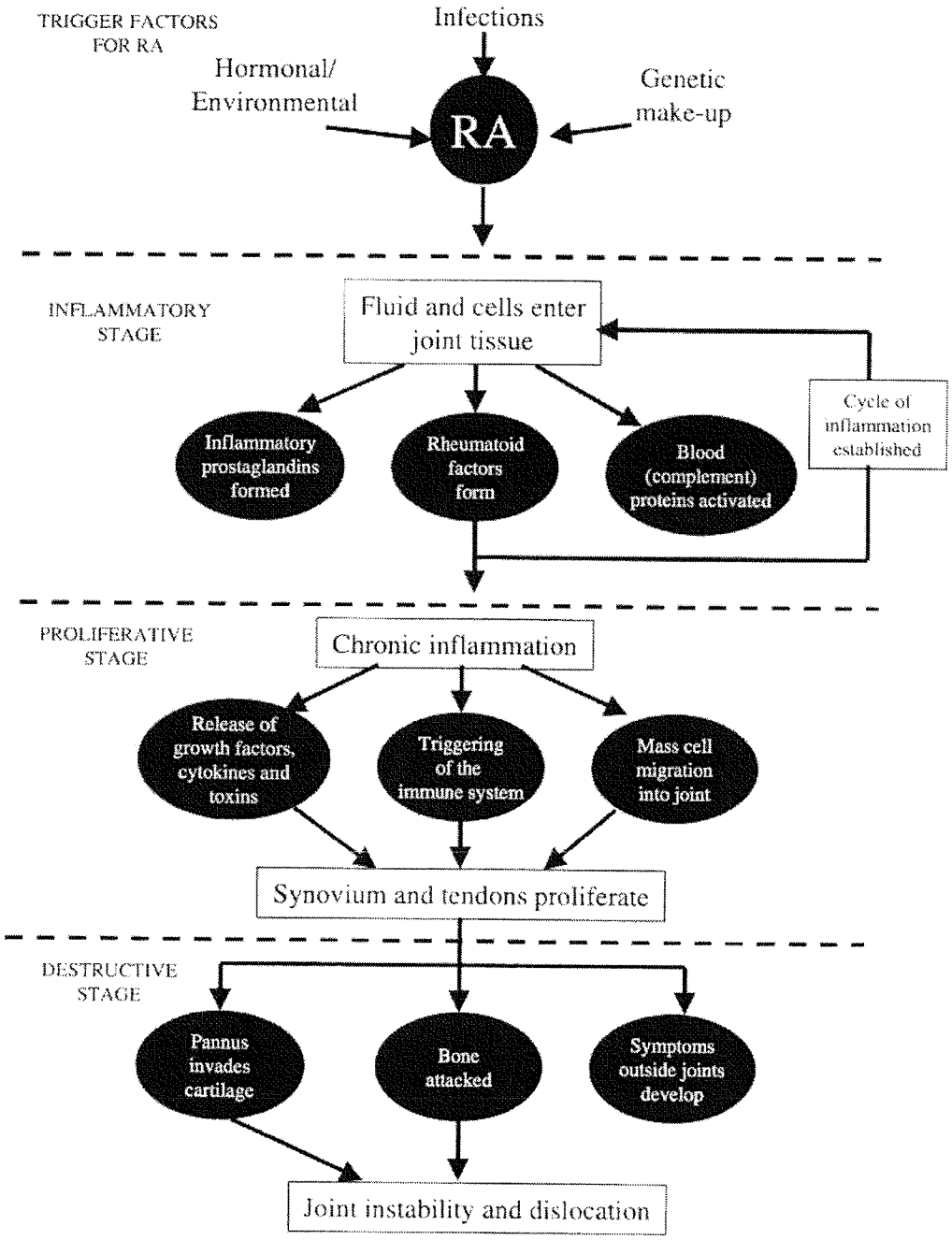
- The inflammatory stage which is characterised by pain, swelling, stiffness and early bone loss (a period of a few months to a few years). The synovium shows evidence of a chronic inflammatory reaction and there is infiltration of lymphocytes, plasma cells and macrophages

- The proliferative stage in which the synovium and tendons around the joint thicken and form an invasive pannus (a tumour-like mass)

- The destructive stage in which cartilage and bone are eroded, the joints become unstable and may dislocate resulting in characteristic deformities. The pannus tissue and the synovium now contain a variety of cell types. These cells release digestive enzymes that break down cartilage and bone

These stages of development are summarised graphically in Figure 2.4.

Figure 2.4: Stages in the progression of rheumatoid arthritis



Source: Target Rheumatoid Arthritis, 1997

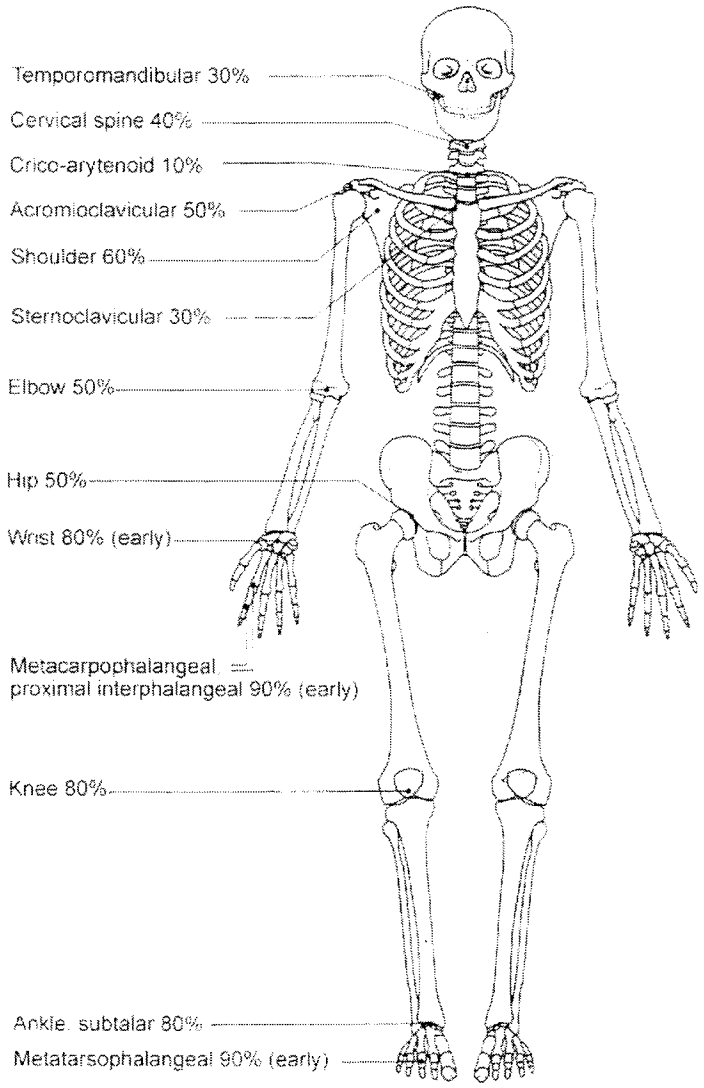
Once cartilage has been lost, the damage cannot be reversed and progression of the disease is inevitable. Eventually, the inflammation will subside and the symptoms change to pain later in the day and less morning stiffness. Once the joints have become deformed, the patient's ability to function deteriorates accordingly.

2.4.6.1 Articular disease

Involvement of the hands and wrists is common as is that of the elbow and shoulder, knee, ankle and foot. The hip is seldom involved in early rheumatoid arthritis but may be affected later. Similarly, the cervical spine becomes important in long-term disease affecting the atlanto-axial joint.

The joint sites affected in established rheumatoid arthritis are shown in Figure 2.5.

Figure 2.5: Involvement of joint sites in established rheumatoid arthritis



Source: Reproduced from Brooks P M. Rheumatoid Arthritis. Medicine 1998; 26:6:30 by kind permission of The Medicine Publishing Company.

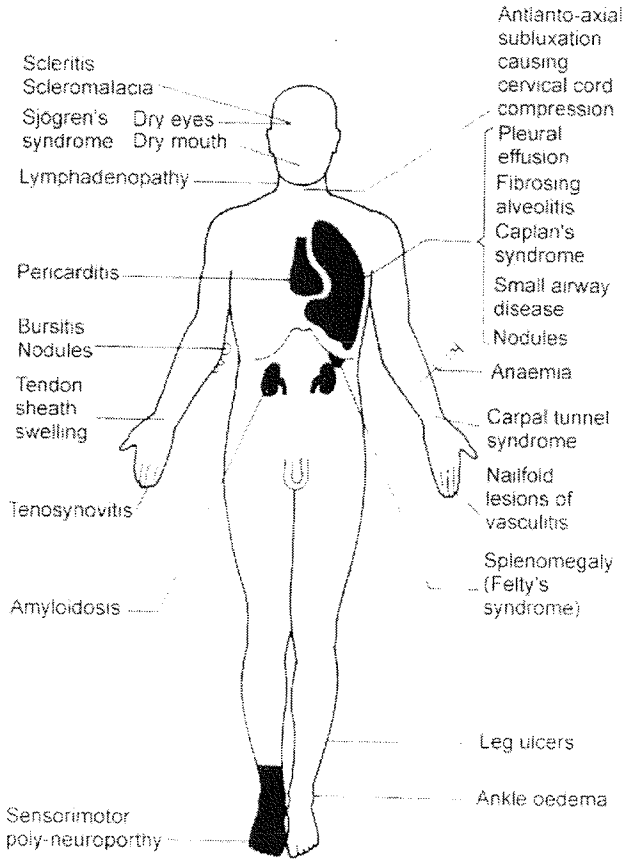
2.4.6.2 Extra-articular disease

Rheumatoid arthritis is systemic in nature and affects not only joints, but also almost any other organ and it can be responsible for a whole range of malfunctions. These include:

- Haematological disorders (anaemia and neutropenia)
- Pulmonary disorders (pleuritis/pleural effusion, pneumonitis, pulmonary nodules, interstitial lung disease)
- Cardiac involvement
- Neurological problems (compressed neuropathies eg carpal tunnel syndrome)
- Vasculitis
- Rheumatic nodules
- Skin disorders
- Ocular involvement
- Renal disease (more related to therapy for the arthritis itself)

Non-articular manifestations of rheumatoid arthritis are indicated in Figure 2.6.

Figure 2.6: Non-articular manifestations of rheumatoid arthritis



Source: Kumar P J and Clark M L (Eds). Clinical Medicine, Second Edition, 1990. W B Saunders: London. Published with permission.

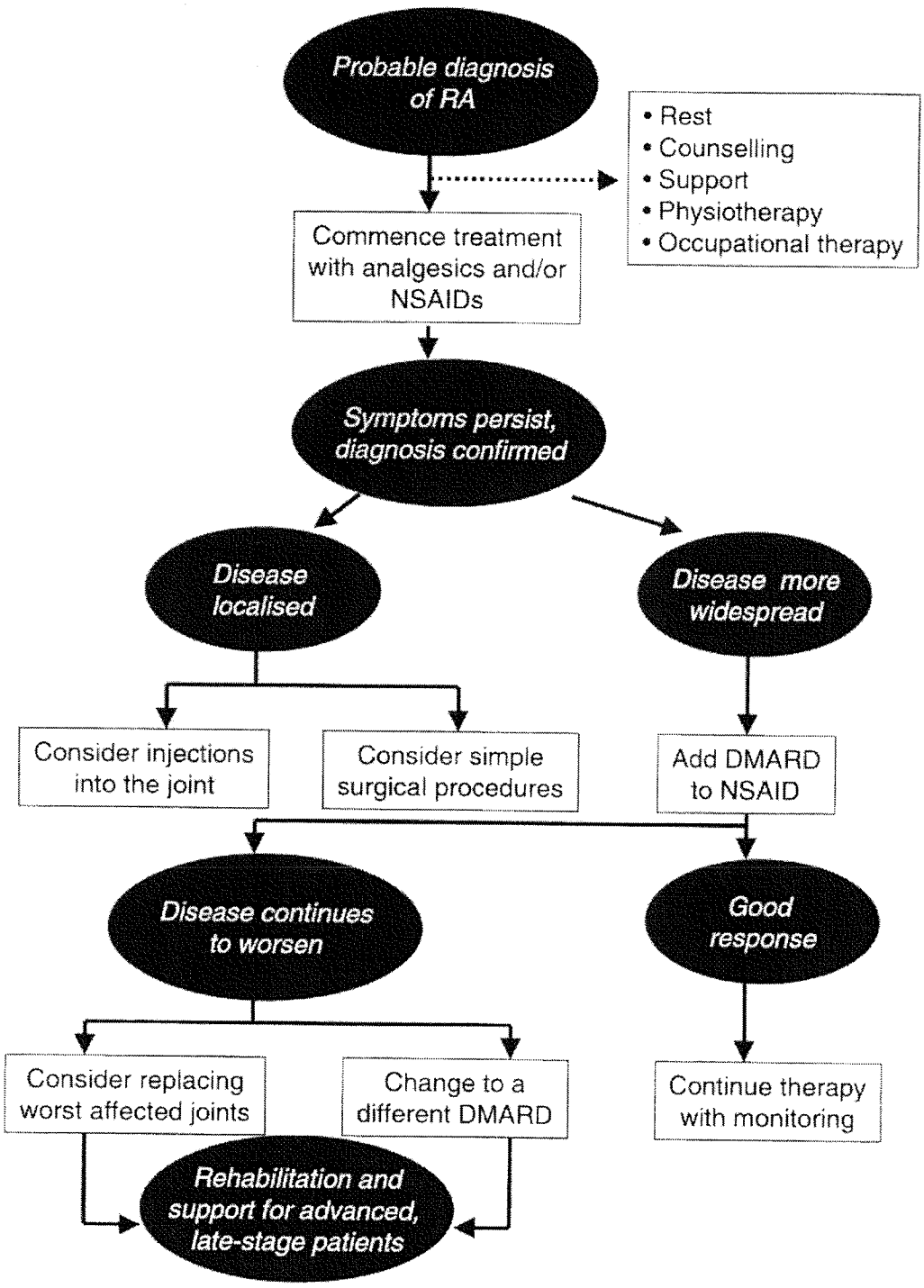
2.4.6.3 Prognosis

The prognosis depends on a number of factors, including the severity of the disease at the start, whether a high titre of rheumatoid factor is present, whether the patient has the gene HLA DR4 and whether the patient is a woman. It can cause severe disability in about 5% of cases and for these people life expectancy is reduced. Treatment helps to slow the rate at which disability develops (http://easyweb.co.uk~pgardiner/ra_arth.htm).

2.4.7 Management of rheumatoid arthritis

Rheumatoid arthritis carries significant morbidity and mortality and because disease progression is rapid in the early phases (van der Heijde *et al.* 1992) it needs to be treated aggressively from the outset. Since there is no cure for the disease, the aim of its management is to achieve complete remission with cessation of fatigue, relief of pain, prevention of deformity and maintenance of normal function (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996). The approach to disease management is summarised in the algorithm shown in Figure 2.7.

Figure 2.7: The approach to the management of rheumatoid arthritis



Source: Target Rheumatoid Arthritis, 1997.

Basic issues such as education, exercise, physiotherapy and dietary advice all play a role in the management of rheumatoid arthritis. However, once the disease has been diagnosed,

drugs that slow joint destruction and reduce disability, disease-modifying antirheumatic drugs (DMARDs) are given immediately. NSAIDs have no effect on the disease in the long term but are important in providing relief of symptoms, particularly at the outset while waiting for DMARDs to take effect. Analgesics such as paracetamol also play a role in relieving pain and assist in reducing the dose of NSAIDs. Corticosteroids are still used in the management of rheumatoid arthritis in certain situations.

Further to these established therapies, new medicines to control the destructive stage of the disease are now reaching the market (see Chapter 4).

2.4.7.1 Drugs to relieve pain

All rheumatoid arthritis sufferers experience some pain and its management is an important part of the treatment of the disease. NSAIDs are often satisfactory for pain relief but in some instances additional analgesics are required, particularly where gastrointestinal effects are a problem. Simple analgesics such as paracetamol and codeine relieve the pain but are without anti-inflammatory activity. However, combined with NSAIDs means that the NSAID dose can be reduced.

2.4.7.2 Drugs to control the inflammatory response

NSAIDs are generally the first drugs used in the treatment of rheumatoid arthritis. They interfere with the synthesis of PGs and related substances by inhibiting the COX enzyme (see Chapters 3 and 4). These anti-inflammatory drugs do not change the course of the disease itself but they are used to control the symptoms. They reduce joint inflammation, pain, swelling and the fever accompanying the disease.

NSAIDs include aspirin, ibuprofen, indomethacin, ketoprofen, naproxam and a number of newer agents (see Chapter 3). They belong to different chemical classes and their properties depend on the way in which they are absorbed, metabolised and excreted by the body. Furthermore, tolerance to NSAIDs differs between patients and the appropriate NSAID must be found to suit the individual.

The main problem with NSAIDs is their effect, to a greater or lesser degree, on the gastrointestinal tract where they may promote the development of gastric erosions and ulceration. The way in which this can be overcome is to use them in combination with a gastric mucosal barrier protector eg misoprostol (Cytotec). Other serious side effects of NSAIDs are renal toxicity, liver damage, increased fluid retention, rashes and photosensitivity. The extent to which these effects manifest themselves depends, as indicated above, on the drug and on the individual patient.

NSAIDs are discussed further in Chapter 3.

2.4.7.3 Drugs to alter the disease process

Unlike NSAIDs which treat the symptoms of the disease rather than the cause, DMARDs are able to establish remission, although they are not able to reverse the disease process. They do not relieve pain but can reduce or prevent joint damage and maintain mobility and function in as many as two-thirds of patients (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996).

These drugs are a mixed group which act by different mechanisms and have different side effect profiles but they all have the ability to modify the disease process to a greater or lesser extent. Some drugs are more effective than others and increasingly, some patients are treated simultaneously with two or more DMARDs (see Chapter 3). They may also be treated concurrently with NSAIDs and corticosteroids.

Since joint erosion occurs quickly after disease onset, many rheumatologists prescribe DMARDs early and an aggressive approach is now considered appropriate. Early intervention before joint damage occurs provides a better chance of inducing remission and preventing permanent joint destruction and disability. In general it takes 2–3 months for DMARDs to take effect and their benefits often do not become evident until after 6 months. Further to this, these drugs are potentially toxic and there are side effects to consider. Consequently, each patient must be carefully monitored. The medication also needs to be given continuously, otherwise flares occur within 1–2 months of stopping the drug. The aim of therapy is to establish remission not to cure the disease.

DMARDs commonly used in the treatment of rheumatoid arthritis are listed in Table 2.1 Further information about these drugs can be found in Chapter 3.

Table 2.1: DMARDs and their effectiveness

Drug	Effectiveness
Myocrisin (gold injections)	Effective but problematic side effects
Auranofin (oral gold)	Less effective when used alone
Penicillamine (Distamine)	Effective but has problematic side effects
Methotrexate	Definite evidence that it helps
Azathioprine	Reasonable response with rheumatoid arthritis
Cyclophosphamide	Usually reserved for severe cases
Cyclosporin	A good anti-erosive drug
Sulphasalazine (Salazopyrin EN)	Good evidence that it helps
Chloroquine	Less effective when used alone
Hydroxychloroquine sulphate (Plaquenil)	Less effective when used alone

Source: Derived from information available on http://easyweb.co.uk~pgardiner/ra_arth.htm

A new DMARD, leflunomide, launched as Arava in September 1998, is the first DMARD to be launched for the treatment of rheumatoid arthritis for a decade. It is claimed to delay structural joint damage as backed by X-ray evidence (see Section 4.2.1.1). It will be interesting to see how this drug is received in the clinic.

The choice of DMARD varies depending on the patient and on the severity of the disease. Methotrexate is the most widely used regimen because it has a rapid onset of action (3–4 weeks) has a good safety profile and is more beneficial in synovitis. Sulphasalazine is another DMARD with a good safety profile. It is widely used in ulcerative colitis and is gaining popularity for the treatment of rheumatoid arthritis, particularly in Europe. Oral gold is better tolerated than the parenteral form but is less effective. It appears to be more appropriate for patients with mild to moderate symptoms. Plaquenil (hydroxychloroquine) is used for patients with mild, slowly progressing disease and the antimetabolite azathioprine is used mainly for patients with progressive disease that has failed to respond to either methotrexate or gold. Cyclophosphamide and cyclosporine are effective DMARDs but have serious toxic effects. Their use may be restricted to patients who have failed on other DMARDs (see Section 3.2).

2.4.7.4 Combination therapy in rheumatoid arthritis

DMARDs often lose their effectiveness over time and combination therapy is increasingly seen as a way of overcoming this. In fact, there is now apparent universal acceptance for combination DMARD therapy for the treatment of rheumatoid arthritis (O'Dell *et al,* 1997a). This approach is discussed further in Section 3.2.

2.4.7.5 Corticosteroids

Corticosteroids are still commonly used in the management of rheumatoid arthritis and will slow the rate of joint erosion when used as a low-dose regimen. They may be given orally, either as continuous background therapy or as a short course of a rapidly decreasing dose for counteracting disease flares or as an oral pulse dose of 100mg–1g. Alternatively, they may be given parenterally as an intra-articular injection into an inflamed region or as intravenous pulse therapy during a flare or as an induction treatment when commencing DMARDs.

The use of corticosteroids is beneficial but limited by their long-term side effects. These include weight gain, bruising, fluid retention, susceptibility to infection, diabetes and osteoporosis. The incidence of infection is significantly increased even at relatively low doses. Further information about the use of corticosteroids for this indication is given in Section 3.3.

2.5 Some other types of arthritis

2.5.1 Gout

Gout is the most common cause of inflammatory joint disease in men over the age of 40 years (Nuki, 1998). It affects the joints of the feet, especially the big toe but other joints are also frequently involved. It occurs mostly in men and is due to the deposition of excess uric acid in the tissues and blood. Crystals of uric acid deposited in the joints cause inflammation and severe pain. Although there is a genetic component to the disease, environmental factors such as diet, obesity, alcohol consumption and the use of diuretics are important compounding factors. The major determinant of risk for developing the disease is excessive levels of uric acid in the blood stream (Nuki, 1998).

Management in the short term involves the use of NSAIDs (except aspirin) followed by allopurinal (a xanthine oxidase inhibitor) for long-term prophylaxis (Nuki, 1998).

2.5.2 Ankylosing spondylitis

This condition affects primarily the spine or back. The joints and ligaments that support the spine become inflamed and stiff and the bones of the spine may grow together so that the spine becomes rigid and inflexible. Other joints may also be involved, particularly the hips, shoulders, knees and ankles and the heart, lungs and skin may also become affected (Calin, 1998).

Ankylosing spondylitis occurs more often in men than in women with a ratio of 2.7:1. In women it is more likely to involve the peripheral joints while men may have more severe spinal disease (Calin, 1998). Among Caucasion individuals, 0.2–1.0% are affected with the disease (Calin, 1998).

There is a genetic component to the disease with approximately one in five of those affected having a relative with the same disorder. A gene known as HLA-B27 is present in 6–14% of Caucasions and about 95% of those with the disease (Calin, 1998).

The disease is not fatal and provided that it is not left untreated few people with the disease become severely disabled. NSAIDs are indicated for disease management together with daily exercise and general fitness.

2.5.3 Psoriatic arthritis

This is a type of arthritis seen in people with psoriasis or with a family history of psoriasis. Five to eight percent of individuals with psoriasis develop one of several different patterns of arthritis which is typically less severe than rheumatoid arthritis and more limited in distribution. NSAIDs and analgesics and sometimes, corticosteroid injections, are used to control the pain but when the disease is more severe, methotrexate or cyclosporin are given, because they control both the skin lesions and the arthritis. The prognosis is good and usually there is only minimal joint impairment.

2.6 The economics of arthritis

The economic costs of osteoarthritis are considerable. In the US alone, it is anticipated that 1% of gross national product (GNP) will be used for the treatment of osteoarthritis alone by 2000 (Lohmander *et al*, 1996).

The most recent comprehensive economic study of arthritis in the US by Yelin and Callahan (1995) reported the cost of arthritis in the US (including rheumatoid arthritis, osteoarthritis and all other rheumatic conditions), to be $64.8 billion in 1992. Of this, direct costs were estimated at $15.2 billion and indirect costs as $49.6 billion. The cost of rheumatoid arthritis alone was estimated at up to $14 billion per year (see Callahan, 1998).

The cost of illness can be divided into three components: direct costs, indirect costs and tangible costs. Direct costs usually refer to medical care but can also include expenditure for items such as adaptation of the home environment and transportation costs. Indirect costs are commonly calculated as the costs due to lost wages resulting from a reduction or cessation of work. Intangible costs are those derived from loss of function, increased pain and reduced quality of life. They cannot be given a financial value.

A study reported by Lanes *et al* (1997) assessed the cost of care for both osteoarthritis and rheumatoid arthritis patients in a managed care population in the US. Costs were estimated using Medicare reimbursement schedules and average wholesale prices for prescription drugs. The total direct cost of care for rheumatoid arthritis was $703,053 among 325 person-years contributed by 365 rheumatoid arthritis patients. The average individual cost was $2,162 per year. Of this, 62% was attributed to prescription medicines, 21% to ambulatory care and 16% to hospital care.

The total cost of care for osteoarthritis was $4,728,425 in 8,711 person years contributed by 10,101 osteoarthritis patients with an average individual cost rate of $543 per year. The largest component was hospital care (46%) with an average cost of $249 per person-year, mostly due to admissions for hip or knee replacement. Arthritis-related prescription drugs comprised 32% of the total cost ($173 per person-year) and ambulatory care 22%. The care

of osteoarthritis is not expensive on a per patient basis, but the prevalence of the illness is high, which equates to a high cost to the provider.

Detailed studies of the early 1990s showed that the annual cost of rheumatoid arthritis in the UK was approximately $620 million (£380 million) for healthcare services, $100 million (£60 million) for laboratory tests, and $65 million (£40 million) for medicines. Adding indirect costs (loss of income, benefits, social services costs and inflation) brings the present day's annual bill to the region of $1.6 billion (£1 billion) per year (Target Rheumatoid Arthritis, 1997). These estimates are based on a study by McIntosh (1996), described further below.

The total cost of rheumatoid arthritis in England in 1992, was estimated by McIntosh (1996) to be $2.1 billion (£1.26 billion). Of this, $990 million (£604.5 million) or 48.1% of total costs, was direct costs (McIntosh, 1996). The indirect costs, measured as lost productivity due to morbidity, was estimated at $1.067 billion (£651.5 million), 51.9% of the total costs. These costs are broken down as shown in Table 2.2.

Table 2.2: Total economic impact of rheumatoid arthritis in England, 1992

Direct costs	Cost ($)	Cost (£)
Adults in private households - service utilisation		
GP surgery visits	24,422,908	14,917,512
Specialist visits	63,690,237	38,901,997
Home-help costs	98,930,399	60,426,688
Nurse visits	136,220,013	83,203,184
Hospital days	279,554,705	170,752,014
Total	602,818,262	368,201,395
Drug costs	58,427,539	35,687,541
Management of toxicity	95,214,515	58,157,026
Aids (adults in private households)	17,753,846	10,844,049
Adults in communal establishments	215,368,433	131,547,039
Total direct costs	989,582,597	604,437,050
Indirect costs (lost earnings)	1,066,575,471	651,464,298
Grand total	**2,056,158,068**	**1,255,901,348**

Source: McIntosh E. The cost of rheumatoid arthritis. British Journal of Rheumatology 1998; 35, 781–790. Published with permission of the author and Oxford University Press.

Annual direct costs of rheumatoid arthritis in the Netherlands during the first 6 years of the disease were estimated by Van Jaarsveld *et al* (1998). The study was aimed at ascertaining whether annual cost altered with increasing disease duration. The study population was 424 rheumatoid arthritis patients who had participated in a population-based trial on therapeutic strategies for early rheumatoid arthritis since 1990 and were not lost to follow-up in April 1996. A total of 363 questionnaires were analysed. The mean annual direct cost due to rheumatoid arthritis was estimated to be $5,722 (Dfl 11,550) per patient. Medical costs accounted for $3,071 (Dfl 6,198) (55%) and non-medical costs for $2,651 (Dfl 5,352) (45%). Seven cost categories were distinguished as shown in Table 2.3. The costs indicated are an average for all patients studied.

Table 2.3: Annual direct cost of rheumatoid arthritis per patient within the first 6 years of disease duration – a Netherlands study

Cost category	Cost ($)	Cost (Dfl)
Contact with healthcare workers	1,050	2,120
Days in care facilities	1,250	2,524
Medication	562	1,135
Monitoring of side effects	152	307
Alternative medicine	55	112
Adaptations in the home and devices	1,860	3,755
Other costs	791	1,597
Medical costs	3,071	6,198
Non-medical costs	2,651	5,352
Total direct costs	5,722	11,550

Source: Derived from information given in Van Jaarsveld et al, *1998.*

Total mean direct cost was $7,162 (Dfl 14,455) in the first year of the disease, decreasing slightly in the following years but after 4 years, the direct medical costs increased again to $5,528 (Dfl 11,158) per patient in the sixth year.

A summary of four studies, conducted in the US, between the late 1970s and the mid-1980s, published by Callahan (1998) and updated to 1990s values, estimated the annual direct costs of a rheumatoid arthritis patient to be an average $6,000 in 1990 dollars. Hospitalisation rates accounted for 40–60% of direct costs.

Yelin (1996) used similar data to determine the average annual medical care costs among patients with rheumatoid arthritis and updated the estimates to 1994 terms. He estimated costs as $4,328, 50% of which ($2,188) was due to hospital admissions (costs are summarised in 1994 dollars). DMARDs and NSAIDs each accounted for about 8% ($323 and $365 respectively) of the total rheumatoid arthritis-related costs. The absolute indirect costs were estimated to be $3.98 billion.

A Canadian study of direct and indirect medical costs incurred by patients with rheumatoid arthritis revealed annual direct costs of $2,514 ($3,788, 1994 Canadian dollars) in the late 1980s and $3,091($4,656, 1994 Canadian dollars) in the early 1990s (Clarke *et al*, 1997).

A summary of the costs of rheumatoid arthritis derived in these studies is shown in Table 2.4.

Table 2.4: The costs of rheumatoid arthritis ($ per patient per annum)

Study	$ per patient per annum	Country of study
Lanes *et al* (1997)	2,162	US
Van Jaarsveld *et al* (1998)	5,722	Netherlands
Callahan (1998)	6,000	US
Yelin (1996)	4,328	US
Clarke *et al* (1997)	3,091	Canada

The cost to society of arthritis is considerable in all these countries. Any means of reducing its effects could have a major influence on the health of the population and the cost of health services.

CHAPTER 3
ESTABLISHED DRUG THERAPIES

The two categories of drugs used to treat osteoarthritis and rheumatoid arthritis are NSAIDs and DMARDs. These drugs were described briefly within the context of disease management in Chapter 2. The present chapter provides more detailed information and also refers briefly to other drugs which are used to manage these two diseases.

3.1 NSAIDs

Aspirin can be looked upon as the founder member of the group of drugs known as NSAIDs. It was introduced as an anti-inflammatory agent in 1899 but it was to be more than 50 years before powerful and effective alternatives became available. A breakthrough came in the 1960s when Sir John Vane and his colleagues discovered the mechanism of action of aspirin (Vane, 1971). They demonstrated that it blocks COX, the key enzyme in the synthesis of eicosanoids (prostaglandins and related substances) from arachidonic acid. As discussed in Chapters 1 and 2, these are some of the agents involved in the process of inflammation.

The discovery of COX led to the development of a wide range of different NSAIDs and these drugs now probably constitute the most frequently prescribed class of drugs (for any indication). They can be classified into several groups as shown in Table 3.1. The main difference between them is the incidence and type of side effects; the difference in anti-inflammatory effects is small and dependent on the patient. There are also differences in half-life; some have only a short half-life (aspirin, diclofenac, ibuprofen) while others are long acting (oxaprozin, piroxicam, diflunisal). These characteristics will naturally influence the choice of drug.

Table 3.1: Classification of NSAIDs

Class	Subclass	Drug	Comment
Carboxylic acids	Phenylacetic acids	Diclofenac	Similar to naproxen with respect to both action and side effects
		Diclofenac topical	Diclofenac gel – an external formulation with a high degree of activity via the percutaneous route
		Misoprostol + diclofenac	Launched as Arthrotec, a fixed combination of misoprostol (50mg) and diclofenac (0.2mg) for patients with arthritis at risk of gastrointestinal ulcers
		Alcofenac	Similar to naproxen with respect to both action and side effects
		Aceclofenac	Has comparable efficacy and better tolerance compared with other NSAIDs. Twice-daily dosing
	Carbo and heterocyclic acids	Indomethacin	Its action is at least equal to that of naproxen but has a high incidence of side effects (headache, dizziness, gastrointestinal disturbances)
		Glucamethacin	An indomethacin derivative launched as Teoremac in Italy
		Sulindac	Similar in tolerance to naproxen
		Tolmetin	Comparable in effect to ibuprofen
		Etodolac	Comparable in effect to naproxen but side effects comparable to those of ibuprofen

. . . continued

Table 3.1: (continued)

Class	Subclass	Drug	Comment
	Salicylic acids	Aspirin	Traditionally first choice but now NSAIDs are prescribed which are better tolerated and more convenient for the patient
		Diflunisal	An aspirin derivative but its clinical effect is more like that of the propionic acid derivatives. Has a long duration of action which allows twice-daily administration
		Benorylate	Aspirin-paracetamol ester
	Propionic acid derivatives	Ibuprofen	Ibuprofen has fewer side effects than other NSAIDs but its anti-inflammatory properties are weaker. Doses of 1.6–2.4g daily are needed for rheumatoid arthritis
		Dexibuprofen	The S-(+)-isomer of ibuprofen which is expected to be associated with fewer side effects than ibuprofen
		Fenbufen	Claimed to be associated with less gastrointestinal bleeding but there is a high risk of rashes
		Ketoprofen	Has anti-inflammatory properties similar to ibuprofen but has more side effects
		Fenoprofen	As effective as naproxen but associated with slightly more gastrointestinal side effects than naproxen
		Flurbiprofen	Similar profile to fenoprofen. A transdermal flurbiprofen patch has been launched in Japan
		Loxoprofen	Equipotent with indomethacin but possibly fewer side effects
		Naproxen	One of the first choices for the treatment of arthritis. It combines good efficacy with a low incidence of side effects. Naproxen betainate is a combination of naproxen with betaine and has analgesic and anti-inflammatory activity. It has fewer gastrointestinal side effects than naproxen sodium
		Oxaprozin	Oxaprozin is a long-acting, once-daily NSAID. It is as effective as ibuprofen but skin rash and gastrointestinal complaints are common. As a result of its long half-life, it takes several days to reach a steady state
		Tiaprofenic acid	As effective as naproxen but has more side effects
	Fenamic acids	Meclofenamic acid	Meclofenamate sodium is a potent, non-steroidal, anti-inflammatory anthranilic acid derivative, related to mefenamic and flufenamic acids. Gastrointestinal blood loss appears to be less frequent than with indomethacin or aspirin
		Mefenamic acid	An analgesic with minor anti-inflammatory properties. An additional side effect is diarrhoea and occasionally haemolytic anaemia
Enolic acids	Oxicams	Piroxicam	As effective as naproxen and has a prolonged action permitting once-daily administration. It has more gastrointestinal side effects than ibuprofen. Piroxicam cinnamate is the prodrug of piroxicam, it is also a once-daily therapy

. . . continued

Table 3.1: (continued)

Class	Subclass	Drug	Comment
		Meloxicam	The tolerability of meloxicam is believed to be due to the preferential inhibition of COX-2 over COX-1. However, its claim to true COX-2 specificity has been challenged and disputed (see Section 3.1.2.1)
		Teonxicam	Similar in activity and tolerance to naproxen. It has a long half-life which permits once-daily dosing
		Lornoxicam	Short half-life, well tolerated but some gastrointestinal side effects
Non-acidic Compounds		Nabumetone	Comparable in effect to naproxen

NSAIDs are effective in decreasing the inflammatory response and relieving the pain associated with arthritis but have little or no effect on the disease process. Thus with respect to rheumatoid arthritis, they treat the symptoms (ie pain and inflammation) but are unable to prevent joint destruction or organ damage.

3.1.1 Side effects of NSAIDs

The major disadvantage of NSAID therapy is the tendency of these drugs to damage the lining of the stomach, leading to ulceration and on occasions to severe bleeding. The minor side effects of these drugs include abdominal pain and vomiting. A study reported by Ramey *et al* (1996a) evaluated the event rates for all NSAID-induced complications in 1,921 patients with rheumatoid arthritis using data from eight ARAMIS (Arthritis, Rheumatism and Ageing Medical Information System) centres. Information on gastrointestinal complications attributed to NSAIDs was obtained from validated patient reports every 6 months, supplemented by the review of hospital records (where patients were hospitalised). Approximately 15% of patients reported a NSAID-induced gastrointestinal side effect during the 2.5 years of observation and 42 patients had a serious gastrointestinal event which required hospitalisation.

Gabriel and Bombardier (1990) estimated the absolute risk of gastric ulceration as approximately 20%. In their study, the absolute risk for hospitalisation for serious complications was between 0.2% and 4%.

3.1.1.1 Differences in gastrointestinal toxicities of NSAIDs

Significant differences in the gastrointestinal side effects of various NSAIDs were found in a long-term US study presented at the British Society of Rheumatology meeting in Brighton, UK, in April 1998 (*Scrip* 2335, 15 May 1998 p27). Serious gastrointestinal toxicity was defined as gastrointestinal bleeds and other clinically significant events requiring hospitalisation. It was studied for 16 NSAIDs in 9,578 courses (19,289 patient-years). The data, which were collected by the ARAMIS database, are shown in Table 3.2. Serious gastrointestinal events were most frequent with meclofenamate, indomethacin, fenoprofen, piroxicam (Pfizer's Feldene) and flurbiprofen but were not seen with nabumetone (SmithKline Beecham's Relafen) and etodolac.

Table 3.2: Gastrointestinal toxicity of NSAIDs

Drug	Patient-years	Serious gastrointestinal events per 100 patient-years	Incidence per 100 patient-years
Nabumetone	221	0	0.00
Etodolac	88	0	0.00
Salsalate	431	4	0.68
Sulindac	1,449	12	0.93
Diclofenac	1,042	12	0.93
Ibuprofen	1,999	19	0.94
Ketoprofen	506	7	0.96
Aspirin	6,201	74	1.13
Naproxen	3,364	38	1.20
Tolmetin	484	7	1.23
Flurbiprofen	251	4	1.24
Piroxicam	1,592	24	1.39
Fenoprofen	347	8	1.96
Indomethacin	968	28	2.96
Meclofenamate	297	13	3.53

Source: Scrip *2335, 15 May 1998 p27.*
Note: Incidence per 100 patient-years was adjusted for confounding risk factors, except in the case of nabumetone and etodolac, where no serious gastrointestinal toxicity was observed.

The toxicity index showed that aspirin, salsalate and ibuprofen were the least toxic and meclofenamate and indomethacin the most toxic NSAIDs. This study has also been reported by Fries (1996).

3.1.1.2 Methods of reducing the side effects of NSAIDs

Much effort has been devoted to reducing the undesirable side effects of NSAIDs on the gut. The approaches that have been used are summarised in Table 3.3.

Table 3.3: Methods used to reduce the gastrointestinal side effects of NSAIDs

Method	Type of product
Specially coated tablets or slow-release drugs to reduce contact with the stomach lining	Soluble, coated or slow-release forms of, for example, aspirin, diclofenac, flurbiprofen, ibuprofen and indomethacin are available with improved tolerance in the stomach. Companies involved include Knoll, Eli Lilly, Napp, Novartis, Parke-Davis and Trinity
The development of drugs that heal stomach ulcers that can be taken together with NSAIDs and tablets containing a combination of NSAIDs with a substance which protects the stomach	A combination pack of naproxen and tablet of misoprostol (to protect the stomach against the ulcer-inducing action of naproxen). A reduction of 40% in stomach complications has been reported. The product is marketed by Searle Searle has extended this approach to the development of a combination of diclofenac and misoprostol as a single tablet marketed as Arthrotec. With this product, the risk of stomach ulcers has been shown to be reduced by up to two-thirds compared with diclofenac alone
More selective drugs that only block COX-2	The search has begun for selective COX-2 inhibitors and these drugs are now arriving on the market (see Section 4.1). One NSAID, meloxicam, developed by Boehringer Ingelheim, appears to inhibit COX-2 at lower concentrations than COX-1. It is more selective than the earlier NSAIDs and has fewer side effects but is still not classed as a selective COX-2 inhibitor

Source: Based on information derived from Target Rheumatoid Arthritis, 1997.

Misoprostol (Cytotec) is a synthetic analogue of PGE_1 which protects the gastroduodenal mucosa against numerous aggressive factors. It acts in a similar manner to PGE_1 to increase mucus and bicarbonate secretion and to increase mucosal blood flow. It also inhibits acid secretion by acting on the parietal cells (acid secreting cells).

Misoprostol replaces natural PGs that are suppressed by NSAIDs, thus protecting the gastric mucosa from injury.

Searle's diclofenac/misoprostol combination product, Arthrotec, has now been launched in the US for the management of osteoarthritis and rheumatoid arthritis in patients at high risk of gastrointestinal ulcers. The product was first launched in Canada and Europe in 1993 and is now available in over 40 countries including the UK, Germany, Sweden, the Netherlands and Canada (*Scrip* 2298, January 1998 p18).

Studies show that Arthrotec therapy has a 65–80% lower incidence of NSAID-induced ulcers when compared with other NSAID therapies, including ibuprofen and naproxen. The effective dosing level is 50mg or 75mg diclofenac sodium/200µg misoprostol taken once or twice daily. Searle filed a new drug application (NDA) for Arthrotec in January 1996. The FDA required US clinical trials and did not accept European registration trials, which accounts for the time gap between the US and overseas approvals.

An important development in the progress of NSAID research was the discovery of two isoforms of the COX enzyme, a constitutive form and an inducible form which is present only in injured and inflamed tissue (see Chapter 1). It is now known that inhibition of COX-1 accounts for many of the side effects of the NSAIDs, in particular their gastrointestinal toxicity, and it is the inhibition of COX-2 that produces the anti-inflammatory response. The established NSAIDs do not distinguish between the two isoforms of the enzyme and therefore, pharmaceutical research has been directed towards the development of COX inhibitors that selectively inhibit COX-2 but have no effect on COX-1. The progress being made in this area is discussed in Chapter 4.

3.1.2 COX selectivity of current NSAIDs

The COX-1/COX-2 selectivity of some widely used NSAIDs was examined by Cryer & Feldman (1998) in 16 healthy volunteers. They showed that some NSAIDs (eg flurbiprofen and ketoprofen) were COX-1 selective, some (eg ibuprofen and naproxen) were essentially non-selective and others (eg mefenamic acid and diclofenac) were COX-2 selective. However, even the so-called COX-2 selective agents still had sufficient COX-1 activity to cause potent inhibition of gastric PGE synthesis at concentrations achieved *in vivo*. Their study emphasises the point that, among the established NSAIDs, there are no truly selective COX-2 inhibitors.

3.1.2.1 The debate regarding meloxicam

Boehringer Ingelheim claim that the NSAID, meloxicam (Mobic), is a more selective inhibitor of COX-2 than COX-1 and so should, in theory, have a better side effect profile than NSAIDs which inhibit both COX-1 and COX-2. The company has submitted a US approval application for Mobic, for the treatment of osteoarthritis, claiming it to be a selective COX-2 inhibitor and therefore to have less gastric toxicity than other NSAIDs. However, other companies claim that it is not a true selective COX-2 inhibitor (*Scrip* 2400, 6 January 1999

p22) and it has been suggested that the product may actually be a 'COX-2 preferential inhibitor' rather than a true COX-2 selective inhibitor (*Scrip* 2286, 21 November 1998 p20).

Two major, recently published studies, MELISSA and SELECT, suggest that, nevertheless, meloxicam does have better gastrointestinal tolerability than other NSAIDs (*Scrip* 2381, 23 October 1998 p22). In these two trials, which are the largest prospective double-blind trials of NSAID tolerability in osteoarthritis to date, meloxicam was compared with diclofenac and piroxicam. The results of MELISSA, involving more than 9,000 patients in 27 countries and SELECT, involving more than 8,500 patients in 12 countries were published recently by Hawkey *et al* (1998). Their findings support the preliminary results from the trials which were reported last year at the International League against Rheumatism in Singapore (*Scrip* 2258, 15 August 1997 p18).

In the MELISSA study, patients were randomised to either 7.5mg of meloxicam or 100mg of diclofenac sustained release, administered once daily for 28 days. Patients on meloxicam had 32% fewer (13% versus 19%, $p<0.001$) gastrointestinal adverse events (including dyspepsia, nausea, vomiting, abdominal pain and diarrhoea) than patients receiving diclofenac. In addition, only three patients on meloxicam were hospitalised for a total of 5 days, because of adverse gastrointestinal events, compared with ten patients on diclofenac who spent a total of 121 days in hospital.

In SELECT, patients were randomised to 7.5mg of meloxicam or 20mg of piroxicam once daily for 28 days. Meloxicam-treated patients had 33% fewer (10.3% versus 15.4%, $p<0.001$) gastrointestinal adverse events than those on piroxicam.

References to Phase III clinical trials with meloxicam are to be found in a recent review by Hawkey (1999).

In early 1999, the US Food and Drug Administration's (FDA's) arthritis advisory committee said that more studies were required to show that COX-2 inhibitors have fewer gastrointestinal side effects than non-selective NSAIDs (*Scrip* 2322, 1 April 1998 p20). The new results for meloxicam could, it is thought, be used to support the selectivity claims.

Another point of note is the warning by Boehringer Ingelheim about gastrointestinal and skin reactions in meloxicam's summary of product characteristics. This warning followed reports of 'serious reactions' to it in the UK publication, Current Problems in Pharmacovigilance (see *Scrip* 2368, 9 September 1998 p31).

3.2 DMARDs

DMARDs continue to be the mainstay of rheumatoid arthritis treatment. Unlike NSAIDs, they do not produce immediate benefit. The time from first taking the drug to first seeing an effect is between 4 weeks and 3 months and 4–6 months of treatment are required before a full response is seen. Hence their alternative name, 'slow acting agents'. They are effective in reducing pain and stiffness and improve not only the symptoms and signs of rheumatoid arthritis, but also its extra-articular manifestations. However, there is no evidence that they can induce true remission or alter the long-term outcome of the disease. They decrease the ESR and sometimes, the rheumatic factor titre. Some may even retard the erosive damage of the joint. However, despite their effectiveness, they cannot cure the disease and most patients commenced on a DMARD will not be taking that particular drug 3–4 years later. This is

likely to be due to either an adverse drug reaction or to the fact that the drug is no longer effective.

The DMARDs currently available have been in use for the management of rheumatoid arthritis for many years. They are all chemically different from each other and in the main, were not designed primarily as anti-inflammatory drugs. The way in which they work is unclear but they all impact on the proliferative stage of the disease and have the potential to limit damage to the joints. All the drugs have a significant level of adverse effects.

Table 3.4 lists the DMARDs commonly used in the treatment of arthritis, their route of administration and their potential side effects.

A wide range of studies has been published which demonstrates the effects of this assorted group of drugs on proinflammatory cytokine production, immune cell activation and proliferation, effector cell responses, enzyme inhibition and signal transduction pathways (reviewed by Danning & Boumpas, 1998).

Table 3.4: DMARDs used in the treatment of rheumatoid arthritis

Type of drug	Generic name	Trade name	Dose	Side effects
Gold	Sodium aurothiomalate	Myocrisin (Rhône-Poulenc Rorer)	By deep intramuscular injection initially as a test dose of 10mg (to make sure that the patient is not allergic to it) followed by regular weekly doses of 20–50mg. After a cumulative dose of 1g the dose may be reduced to fortnightly or monthly	Severe reactions in up to 5% of patients (can be fatal); mouth ulcers; skin reactions; proteinuria; blood disorders (sometimes sudden and fatal)
	Auranofin	Ridaura (Bencard)	6mg daily increasing to 9mg in two divided doses if the response is inadequate after 6 months	Diarrhoea and stomach upsets. Skin rashes, pruritis, metallic taste and mouth ulcers are uncommon but if persistent may be an indication to stop therapy
Penicillamine	Penicillamine	Penicillamine (non-proprietary); Distamine (Dista); Pendramine (ASTA Medica) Cuprimine (Merck & Co)	125–250mg daily for 1 month, increasing by similar amounts at not less than 4-weekly intervals to a maintenance dose of 500–750mg daily	Common initial side effects are nausea, anorexia, fever and skin reactions. The main side effects requiring cessation of therapy are skin rashes, mouth ulcers, glomerulonephritis and thrombocytopenia. Rare adverse events are immune abnormalities such as drug-induced lupus, pneumonitis and myasthenia gravis
Immuno-suppresants	Methotrexate	Methotrexate (non-proprietary) Rheumatrex (Wyeth-Ayerst)	Once weekly oral dose of 7.5mg as a single dose or as three divided doses at intervals of 12 hours. A maximum total weekly dose of 20mg	Nausea; abdominal discomfort; inflammation of the lung; mouth ulcers; skin rashes or infections; drop in blood count; hepatotoxicity; bone marrow suppression; pneumonitis; megaloblastic anaemia; nausea; vomiting. Methotrexate is teratogenic

... continued

Table 3.4: (continued)

Type of drug	Generic name	Trade name	Dose	Side effects
	Azathioprine	Azathioprine (non-proprietary) Imuran (Glaxo Wellcome)	3mg/kg daily reduced according to response. Maintenance dose: 1–3mg/kg daily	Oncogenicity; cytopenia
	Cyclophosphamide	Cyclo-phosphamide (non-proprietary); Endoxana (ASTA Medica)	1–1.5mg/kg daily orally. May also be given intravenously in a dose of 0.5–1g for severe systemic rheumatoid arthritis	Interstitial nephritis and haemorrhagic cystitis; oncogenicity; neutropenia; alopecia; teratogenic effects
	Cyclosporin	Neoral (Novartis); Sandimmun (Novartis)	Initially 2.5mg/kg daily in two divided doses, if necessary, increased gradually after 6 weeks to a maximum of 4mg/kg daily. The maintenance dose is adjusted according to response	Renal impairment; hypertension; lymphoma
Sulphasalazine	Sulphasalazine	Salazopyrin EN	Initially 500mg daily increased by 500mg at intervals of 1 week to a maximum of 2–3g daily in divided doses	Skin rash, cough, headache, nausea, depression or irritability; anorexia; dizziness, hepatic reactions, neutropenia; oligospermia
Antimalarials	Chloroquine	Avloclor; Nivaquine	150mg daily (maximum 2.5mg/kg daily)	Gastrointestinal disturbance, rash, headache, convulsions, visual disturbances, irreversible retinal damage, corneal opacities
	Hydroxy-chloroquine sulphate	Plaquenil	400mg daily	As chloroquine

3.2.1 Current DMARDs

3.2.1.1 Methotrexate

The cytotoxic drug, methotrexate, is often the first DMARD of choice for treating rheumatoid arthritis because it has the most predictable benefit (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996; O'Dell, 1997b). It is given once a week (7.5–15mg), either orally or by injection and produces significant anti-inflammatory effects within 3–4 weeks. It is one of the best tolerated DMARDs with more than 50% of patients who take it doing so for longer than 3 years (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996). Its anti-inflammatory effects involve a reduction in inflammatory leukotrienes, suppression of cell-mediated immunity, modification of the expression of the gene encoding for collagenase and blocking the proliferation of synovial fibroblasts and endothelial cells. The disadvantages of methotrexate are listed in Table 3.4. The most serious side effects are neutropenia and liver toxicity, for which monitoring procedures need to be carried out. Additionally, methotrexate can damage the lungs and cause nausea, diarrhoea, hair loss and mouth ulcers (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996).

The mechanism of action of methotrexate is traditionally assumed to be due to its activity as a folate analogue and subsequent inhibitor of dihydrofolate reductase. This inhibition results in a deficiency of the reduced folate substrates required for the synthesis of purines and pyrimidines and consequently, for the synthesis of nucleic acids. However, there is doubt as to whether this is indeed the major mechanism responsible for the anti-inflammatory and immunomodulatory effects of this drug and a number of other explanations have been proposed (see Danning & Boumpas, 1998).

3.2.1.2 Cyclosporin

Cyclosporin is an immunosuppressive agent which was discovered in 1972 and has been used extensively in human subjects since 1978. It is effective in rheumatoid arthritis and is promising for patients with prognostic markers for the development of severe disease but it has serious side effects, for example, nephrotoxicity (Cranney & Tugwell, 1998). It is more selective than methotrexate in that it acts reversibly and specifically on lymphocytes, blocking the proliferation of CD4+ T-cells and consequently the release of inflammatory cytokines and cytotoxins. The primary action of cyclosporin on the immune system is the inhibition of IL-2 synthesis and expression. It also blocks the expression of the CD40 ligand which is found on activated T-cells and is necessary to stimulate the proliferation of B-cells (Fuleihan *et al*, 1994).

The use of Neoral, a microemulsion formulation of cyclosporin, in rheumatoid arthritis has been reviewed by Cranney and Tugwell (1998). The review includes information on randomised placebo trials, comparative studies and combination studies.

3.2.1.3 Antimalarials

The use of antimalarials (chloroquine and hydroxycloroquine) for the treatment of rheumatoid arthritis is covered in a series of articles referred to by Li *et al* (1998). The article also reports studies regarding their toxicity.

An important feature of these antimalarial drugs is their high accumulation and storage in tissues. Their mechanism of action has long been thought to be related to their accumulation within the lysosomes where they generate a shift in pH and render the acid-proteases therein, ineffective (MacIntyre & Cutler, 1988). Since the lysosomal enzymes are involved in a variety of cellular functions, for example, the recycling of receptors to the cell surface, it has been suggested that their antirheumatoid effects could be mediated via this mechanism (see Danning & Boumpas, 1998). According to Danning and Boumpas, several authors have reported the decreased production of various proinflammatory cytokines after stimulation with chloroquine or hydroxychloroquine. Other cellular functions reported to be affected by antimalarial drugs include chemotaxis and superoxide production from neutrophils, antigen processing and presentation and the regulation of PLA_2 (and consequently, arachidonic acid release). The review by Danning and Boumpas provides numerous references on this subject.

Hydroxychloroquine inhibits the movement of granulocytes and slows the process of phagocytosis. It also slows cartilage destruction and prevents the formation of the antigen-antibody complexes that promote the immune reaction in the diseased joint (Borigini & Paulus, 1995). It benefits 60–70% of rheumatoid arthritis patients but its clinical effects are not apparent for 3–6 months and it may take a year before its maximum potential is achieved (Borigini & Paulus, 1995). Despite its relative safety, hydroxyquinoline often causes nausea, vomiting, gastrointestinal pain and diarrhoea. Skin rashes are also an undesirable side effect (see articles referred to by Li *et al*, 1998).

3.2.1.4 Sulphasalazine

Sulphasalazine contains the antibacterial drug sulphonamide. It continues to be used extensively in the treatment of rheumatoid arthritis. It has relatively poor absorption from the gastrointestinal tract with most of it being cleaved by intestinal bacteria into its two components, 5-aminosalicylic acid and sulfapyridine (Smedegard & Bjork, 1995). It has been shown that sulfapyridine can inhibit the growth of several bacteria, decreasing the load of potential antigens, but it is not thought that this is the main mechanism of action of the drug. Sulphasalazine has been noted to be an inhibitor of folate metabolism (a dihydrofolate reductase inhibitor) leading to a decrease in cell proliferation and it has been shown to inhibit the proliferation of T- and B-cells and immunoglobulin synthesis (see Danning & Boumpas, 1998, for references). It has also been shown to reduce the release of a number of cytokines including IL-1, IL-2, TNF-α, IL-6 and IFN-γ (references in Danning & Boumpas, 1998). Other suggested mechanisms of action are also reported by these authors.

Sulphasalazine may cause skin rashes but the most serious potential adverse effect is neutropenia.

3.2.1.5 D-penicillamine

D-penicillamine is an established DMARD which has been in use for many years. It is related to penicillin. Its action with respect to rheumatoid arthritis is not known but it inhibits the function of T-cells. Its toxic effects limit it to use only after methotrexate or another DMARD has failed. It may require more than 12 weeks to have an effect. There are potentially serious side effects, including blood toxicity and renal damage which necessitates close monitoring (Borigini & Paulus, 1995).

3.2.1.6 Gold

Gold-containing drugs are used to treat patients with rheumatoid arthritis present in several joints, which progresses despite prior treatment. Although gold exists as an insoluble element, once oxidised, the gold ion can be stabilised in solution and can be administered either orally or as an intramuscular injection. The efficacy of gold salts has been well documented but their mechanism of action remains largely unknown.

Gold-containing drugs have been found to decrease T- and B-cells in rheumatic joints and reduce the production of immunoglobulins (including the antibodies that promote joint inflammation). They also act against the complement proteins and may restrict the ability of immune cells to produce IL-1.

As a therapy, oral gold is easier to administer than the injectable form but it takes longer to act. Intramuscular gold is effective within 3 to 6 months in up to 80% of patients (Borigini & Paulus, 1995). The most common side effects of the oral therapy are gastrointestinal discomfort, pruritis and oral ulcers. Injectable gold-containing drugs are associated with kidney and liver damage, thromboyctopenia and severe anaemia. Gold therapy is usually stopped within 5 years because of side effects or because it is no longer effective.

Clinical trials and adverse reactions to gold therapy are covered by a number of reviews quoted in Li *et al*, 1998. Potential mechanisms of action which might be attributed to gold therapy are reviewed by Danning and Boumpas (1998).

3.2.2 Combination therapy

In 1997, combinations of DMARDs were used by 99% of the rheumatologists in the US to treat an estimated 24% of all rheumatoid arthritis patients (O'Dell, 1997a). These figures have increased significantly in the last 2 years. However, this near total acceptance of combination DMARD therapy is a recent approach, since in 1994, opinions were the reverse. Reasons for the evolution of combination therapy are as follows:

- Most DMARDs lose their efficacy with time
- The response to a single DMARD is often suboptimal
- Toxic side effects of one DMARD may be played down by using lower doses in combination therapy
- Combination therapy is now proven to be safer and more effective that mono therapy (see O'Dell, 1998)

Until recently, scientific evidence to support the advantages of this approach was lacking but this is no longer the case and an increasing number of high-quality trials have now been published. These are reviewed by Verhoeven *et al* (1998).

The first major publicised study of triple therapy was that of O'Dell *et al* (1996) which demonstrated the effectiveness of triple combination therapy using a combination of methotrexate, sulphasalazine and hydroxychloroquine. The study was a 2-year double-blind randomised study of 102 rheumatoid arthritis patients who had responded poorly to at least one DMARD. The arms of the study were methotrexate alone (7.5–17.5mg per week,

adjusted in an attempt to achieve remission), a combination of sulphasalazine (500mg twice daily) and hydroxychloroquine (200mg twice daily) or a combination of all three drugs. The primary endpoint of the study was the successful completion of 2 years of treatment with 50% improvement in symptoms of arthritis and no evidence of drug toxicity. The findings showed that 49% of the patients had 50% improvement at 9 months and maintained at least 50% improvement for 2 years without evidence of major drug toxicity. Among them were 77% of patients treated with all three drugs (24 of 31), 33% with methotrexate alone (12 of 36) and 40% of those treated with sulphasalazine plus hydroxychloroquine (14 of 35). Drug toxicity caused seven patients in the methotrexate group, and three patients in each of the other two groups to discontinue treatment.

Overall the study showed that a sulphasalazine-hydroxychloroquine-methotrexate combination treatment was significantly more effective than using either methotrexate alone or a combination of methotrexate-sulphasalazine.

O'Dell (1998) has also reported the results of a long-term follow-up of 60 patients treated with triple therapy for a mean period of 3.3 years. Thirty-one of these patients were randomised to triple therapy in the initial trial and the remaining 29 were treated with triple therapy after suboptimal responses to the initial protocol. There was a 50% improvement in 44 (73%) of patients and 17% failed to gain improvement (10% withdrew because of side effects).

According to O'Dell (1998), the most commonly used combinations of methotrexate/hydroxychloroquine, methotrexate/sulphasalazine and sulphasalazine /hydroxychloroquine are prescribed by 99%, 84% and 63% of US rheumatologists respectively. Furthermore, 67% of rheumatologists use combinations of at least three DMARDs to treat a subset of their patients (O'Dell, 1997a).

Fries (1996) also demonstrated, with information from ARAMIS, that the relative toxicities of DMARDs is similar overall to the NSAIDs and that using combination therapy does not increase their relative toxicity profiles. The use of combination therapy would appear to be a promising way forward in the management of this chronic disease.

3.2.2.1 The future of combination therapy

The possible combinations of DMARDs that could be used to treat rheumatoid arthritis are endless, especially if biologicals and corticosteroids are included in the permutations. O'Dell (1998) visualises that, in the short term, methotrexate will continue to hold a central role in combination therapy but that both low-dose steroids and metalloproteinase inhibitors (see Section 5.19) will become increasingly important treatment components. The role of soluble TNF-α receptor protein (see Chapter 4), or other biologicals, is seen to be in combination with the more traditional DMARDs, possibly as an induction therapy. The less expensive and more convenient DMARDs will perhaps be used for maintenance therapy.

Kremer (1998) envisages a new role for methotrexate as a keystone to support other therapeutic interventions. At present, according to Kremer, combinations are arbitrary and driven by economics rather than scientific rationale. Ideally they need to be designed to have a complementary mechanism of action without additive toxicity. However, at present, the toxicity of methotrexate is better understood than its mechanism of action and we are effectively reduced to the 'try it and see' approach bearing in mind the potential toxicity of certain combinations. Kremer (1998) discusses the potential of methotrexate in combination

with the emerging biological therapies and suggests ways in which these combination therapies might be developed.

3.2.3 Measuring the benefits of DMARDs in clinical trials

The policy in the past was to start DMARDs late in the disease when it was thought that the risk:benefit ratio favoured their use. However, it is now known that most erosions occur in the first 2 years and during that time, the immune system abnormality becomes entrenched. Thus the duration of the disease prior to starting a clinical trial is important in assessing the efficacy of a drug with respect to improvement of erosions. If treatment is started too late then there will be no evident benefit with respect to response. Newer studies are showing a reduction in erosion scores, for example, with low-dose prednisolone (Kirwan & Lim, 1996) and with cyclosporin (Pasero *et al*, 1996).

3.2.4 The cost-effectiveness of aggressive treatment with DMARDs

There is strong clinical evidence for starting drug therapy as early as possible in the treatment of rheumatoid arthritis. Yet, despite this, many clinicians are reluctant to prescribe aggressive therapy to patients with early mild disease. However, a recent cost analysis study has demonstrated that aggressive early therapy also has economic benefits (Verhoeven *et al*, 1998). In their study, patients with early active rheumatoid arthritis were treated with either a combination of sulphasalazine, methotrexate and prednisolone (n=76) or sulphasalazine and placebos (n=78). The duration of the trial was 1 year. Prednisolone and methotrexate (or placebos) were stopped after 28 and 40 weeks respectively and sulphasalazine was continued for the trial period. Clinical and cost measures were monitored throughout.

Clinical, radiologic and functional outcomes were significantly improved in the combined therapy group. The average total costs per patient were $5,519 for the combination treatment and $6,511 for the sulphasalazine treatment alone. Outpatient and inpatient care consumed approximately two-thirds of the costs. The cost of drugs for the combination treatment was higher than for sulphasalazine alone but the amount of money spent on other drugs (NSAIDs, analgesics and gastroprotective drugs) was lower ($237 compared with $329).

3.3 Corticosteroids

Corticosteroids have several roles in the treatment of rheumatoid arthritis:

- They can be used early on in the disease to manage inflammation while waiting for DMARDs to have an effect
- They can be used chronically when other drug combinations (NSAIDs plus DMARDs) do not achieve an adequate response
- They can be used in short courses during acute flares to reduce inflammation
- They can be given by intra-articular injection into soft tissue sites to reduce local inflammation

Corticosteroid injections are useful when one or more joints are badly inflamed. They can provide relief of pain, stiffness and swelling for up to 6 months. Pulse doses up to 1g

intravenously on three consecutive days are currently given to suppress severe inflammation while longer term treatment is being initiated.

The adverse effects of corticosteroids are dose-related and may be kept to a minimum by using the lowest effective dose of drug. Adverse effects include fluid retention, weight gain, osteoporosis, hypertension, hyperglycaemia, increased appetite, effects on the central nervous system (CNS), cataracts, glaucoma and increased progression of atherosclerosis.

The mechanisms involved in the immunosuppressive/anti-inflammatory effects of corticosteroids include the inhibition of COX-2 expression (Needleman & Isakson, 1997), the inhibition of leukocyte migration, the suppression of immunoglobulin production and the down-regulation of inflammatory cytokine production (Boumpas *et al.* 1993). Several *in vitro* studies have been reported which show that corticosteroids decrease the production of cytokines from activated cells (see Danning & Boumpas, 1998). Further to this, one of the most widely studied mechanisms of action of corticosteroids on inflammation is the regulation of gene expression at both the transcriptional and post-transcriptional level (Danning & Boumpas, 1998). After entering the cell, corticosteroids bind to a cytoplasmic receptor which functions as a ligand-activated transcription factor which stimulates gene expression either by direct interaction with a specific regulatory area of the gene or by interfering with other transcription factors.

Prednisolone is a synthetic corticosteroid that has been used in the treatment of rheumatoid arthritis since the 1950s. It is usually given together with analgesics and anti-inflammatory drugs and may be given together with DMARDs. It has long-term side effects which limits the dose but there is good evidence to support its use in preventing erosions when used early on in the disease. It may be given orally, intramuscularly or intravenously. It has the advantage over the more potent corticosteroids of permitting finer dose adjustment. The maintenance dose is usually 7.5mg daily. The short-term side effects are nausea, dyspepsia, anxiety and insomnia and increased appetite (leading to weight gain). Long-term effects include Cushingoid appearance, obesity, acne, adrenal suppression, hypertension, myopathy, osteoporosis, cataract and growth retardation in children.

Prednisolone farnesil is a topical steroidal anti-inflammatory agent, jointly developed by Kuraray and Taiho for use in rheumatoid arthritis and osteoarthritis. It consists of prednisolone linked at C-21 with farnesil acid. Prednisolone farnesil penetrates the epidermis to reach the inflamed area and has few systemic side effects at therapeutic doses. It is launched in Japan where it is co-marketed as Farnerate by Dainippon in a 1.4% topical gel formulation and as Farnesone by Taiho for chronic rheumatic pain. A cream formulation for rheumatoid arthritis and osteoarthritis is in Phase III clinical trials.

3.4 Other agents launched for the treatment of arthritis

3.4.1 Hyaluronic acid derivatives

Synvisc (hylan G-F 20) is an elastoviscous fluid that is injected into the knee joint to supplement and restore the lubricating, protecting and shock absorbing properties of synovial fluid in patients suffering from osteoarthritis. This treatment, which is known as viscosupplementation, relieves pain and improves mobility in osteoarthritic knee joints. Synvisc is composed of hylans, unique biopolymers developed by Biomatrix from hyaluronan, the naturally occurring polysaccharide that helps provide the synovial fluid with

elasticity and viscosity. In clinical use, a course of treatment consisting of three injections, can provide pain relief in some patients for up to 6 months or more.

Orthovisc (Anika Therapeutics) is another hyaluronic acid derivative administered as an intra-articular injection for the treatment of osteoarthritis of the knee. It is injected into the joint space three times over a 2-week period to provide viscosupplementation.

Two supplemental hyaluronic acid treatments are on the market that are derived from the combs of roosters – one from the Italian company, Fidia, and the other from the Japanese company, Seikagaku Kogyo. The latter product is launched in Japan as ARTZ by Kaken Pharmaceuticals.

3.4.2 Glucosamine sulphate

Glucosamine sulphate is a glucosamine salt developed by Rotta Research for use in osteoarthritis. It is found in high concentrations in healthy joints and is critical to the integrity of the joint tissues. Its main function is to stimulate cartilage synthesis which in turn promotes joint repair. It is taken orally and acts by initiating the repair of damaged joint tissue. It has an excellent safety record, is well tolerated and does not cause allergic reactions.

CHAPTER 4
EMERGING DRUG THERAPIES

NSAIDs and DMARDs have long been the drugs of choice for the treatment of arthritis but, as indicated in the preceding chapters, they are far from ideal. Consequently there has been a concerted effort to break through the barriers and discover new types of therapy to treat this debilitating disease. Now, several new drugs with novel mechanisms of action are emerging on to the market. The two classes of drugs that are currently receiving the most attention are the new selective COX-2 inhibitors and the anti-TNF agents. These and other emerging drugs are listed in Table 4.1 and discussed below.

Table 4.1: Emerging therapies for arthritis

Trade name	Generic name	Originator	Country of origin	Mode of action
Celebrex	celecoxib	Searle (Monsanto)	US	Selective COX-2 inhibitor
Vioxx	rofecoxib	Merck	US	Selective COX-2 inhibitor
Remicade	infliximab	Centocor	US	Anti-TNF monoclonal antibody (MAb) (human-mouse chimaera)
Enbrel	etanercept	Immunex	US	Anti-TNF (TNF receptor p75 fusion protein)
Arava	leflunomide	Hoechst Marion Roussel	Germany	DMARD (pyrimidine synthesis inhibitor)
Therafectin	amiprilose	Boston Life Sciences	US	Synthetic carbohydrate
Prosorba column	apheresis	Cypress Bioscience	US	Blood filtering device

4.1 COX-2 inhibitors

As discussed in Chapters 1 and 3, the inflammation associated with arthritis is due to the synthesis and release of PGs from arachidonic acid by the action of the COX enzyme. Aspirin and similar NSAIDs reduce PG synthesis by blocking the enzyme. For some years now, a wide range of these anti-inflammatory drugs has been available for the treatment of arthritis. They are among the most heavily used in the world even though their benefits may be disappointing and their side effects deleterious. Consequently, current arthritis drug development and ongoing research is aimed at producing more effective and safer drugs without the deleterious side effects of the current ones. Good progress in this area means that we are now on the verge of a breakthrough with a whole new class of anti-arthritis drugs.

4.1.1 Background to the development of COX-2 inhibitors

In the 1980s, Needleman and colleagues showed that the COX enzyme was increased in inflamed tissue and that it was stimulated by IL-1 in cultured human dermal fibroblasts in a dose-dependent manner (Raz *et al,* 1988). This suggested to them that the effect of IL-1 was mediated mainly, if not totally, via the induction of COX synthesis. In 1990, Needleman's group demonstrated that the COX enzyme could be induced by endotoxin (leucopolysaccharide) and that glucocorticoids (eg dexamethasone) inhibited this endotoxin-stimulated release of PGs (Masferrer *et al,* 1990). However, they also noticed that dexamethasone did not inhibit the formation of baseline PGs. These observations led to the

suggestion that a second COX enzyme existed and in 1991, COX-2 was cloned (O'Bannion *et al,* 1991).

It is now known that COX-1 is present in most tissues as the constitutive or baseline enzyme. It is responsible for the maintenance of the gastric mucosa, platelet function and macrophage differentiation and is involved in renal function. COX-2, on the other hand, is induced by injury and inflammation as, for example, in arthritis.

Evidence from animal models of acute rheumatoid arthritis strongly suggests that the increase in PG production seen in inflamed joint tissues is due to increased expression of COX-2 (Anderson *et al,* 1996). The induction of COX-2 has been reported in both human osteoarthritis-affected cartilage (Amin *et al,* 1997) and in synovial tissue taken from patients with rheumatoid arthritis (Kang *et al,* 1996).

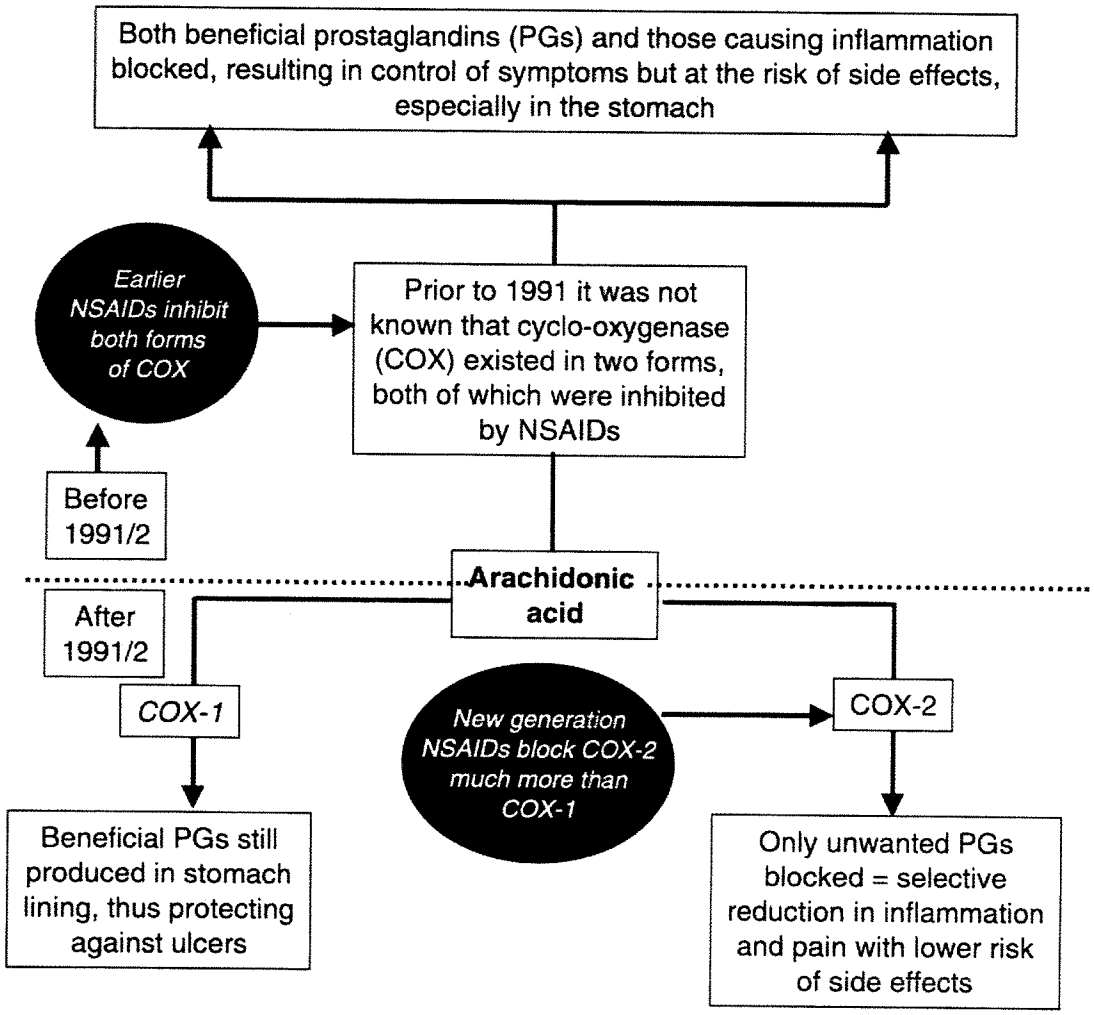
COX-2 has a 60% homology with COX-1 and has the same mechanism of action in that it converts arachidonic acid to PGs but the conditions under which it is present, and its location, differ. Furthermore, COX-1 and COX-2 genes are regulated by two independent and different mechanisms even though the reaction that they catalyse is identical (Dubois *et al,* 1998).

Inhibition of COX-1 accounts for many of the side effects of the NSAIDs, in particular their gastrointestinal toxicity. Serious NSAID-induced gastrointestinal side effects such as stomach perforations, ulcers and bleeding result in more than 76,000 hospitalisations and 7,600 deaths each year in the US alone (*Scrip* 2390, 25 November 1998 pp20–21). In contrast, the inhibition of COX-2 is desirable because it produces an anti-inflammatory response. The established NSAIDs inhibit both forms of the enzyme and consequently, pharmaceutical research has been directed towards the development of COX inhibitors that selectively inhibit COX-2 but have no effect on COX-1.

Two COX-2 specific inhibitors for arthritis are now approaching the market, namely, Searle's celecoxib (Celebrex) and Merck's rofecoxib (Vioxx). Celecoxib was released in the US in January 1999 and is also available in Mexico, Brazil and Switzerland. Additional approvals are pending worldwide. Rofecoxib has been approved in Mexico and the US. Data regarding these two drugs suggest that they will have advantages over regular NSAIDs. The new data have been received enthusiastically by both medical specialists and financial analysts, with both groups prediciting that these new drugs will replace established NSAIDs in the near future. Analysts expect both celecoxib and rofecoxib to quickly become best-sellers and predict sales of more than $1 billion each, and possibly up to $5 billion combined.

Figure 4.1 summarises the relationship between COX-1 and COX-2 and the new generation COX inhibitors.

Figure 4.1: The relationship between COX-1 and the new COX-2 inhibitors



Source: Target Rheumatoid Arthritis, 1997.

4.1.2 Selectivity of COX inhibitors

There has been considerable scepticism about the selectivity of COX-2 agents in the past (*Scrip* 2322, 1 April 1998 p20; *Scrip* 2286, 21 November 1997 p20). The first drugs with this claim, meloxicam (Boehringer Ingelheim's Mobic) and nabumetone (SmithKline Beecham's Relafen) have been marketed as 'COX-2 specific' but are actually 'COX-2 preferential' inhibitors, since they also inhibit the COX-1 enzyme (see Chapter 3). Celecoxib and rofecoxib are a new breed of drugs, and are highly specific for the COX-2 enzyme, showing no inhibition of COX-1 *in vivo* at therapeutic doses and beyond.

4.1.2.1 FDA study recommendations

The FDA arthritis drugs advisory committee has, despite the specificity claimed for the new drugs, said that more studies will be required to definitively show whether selective COX-2 inhibitors really do have fewer gastrointestinal side effects than non-selective NSAIDs. The panel recommended that COX-2 studies should have a placebo comparison and one active

comparator drug in rheumatoid arthritis trials and an active NSAID comparator and a comparison with paracetamol for osteoarthritis studies. Panel members also urged companies to include 3-month endoscopic studies to determine whether erosions or ulcers have developed and to study potential nephrotoxicity, and bone and reproductive effects (*Scrip* 2322, 1 April 1998 p20). The FDA has stated that a drug must show safety in endoscopy studies, that platelet function must not be impaired and that a study of 3 months minimum, with a further 3 months follow-up, will be required to show true efficacy.

4.1.3 Celecoxib

Celecoxib is an orally-active, highly selective COX-2 inhibitor, developed by Searle (Monsanto) as a treatment for rheumatoid arthritis, osteoarthritis and related painful conditions (*Scrip* 2387, 13 November 1998 p12). It is 400-fold more selective for COX-2 than COX-1 (*Scrip* 2175, 25 October 1996 p15).

For osteoarthritis the recommended dose is 200mg per day as a single dose or 100mg twice daily. For rheumatoid arthritis it is recommended at a dose of 100–200mg twice daily (*Scrip* 2400, 6 January 1999 p18).

4.1.3.1 Clinical trials

Celecoxib has been tested in more than 14,000 patients worldwide. The results of Phase III trials and safety data, presented at the ACR meeting in San Diego in November 1998, showed the drug to be as effective as the NSAIDs naproxen and diclofenac for both osteoarthritis and rheumatoid arthritis, but with a superior gastrointestinal safety profile (*Scrip* 2390, 25 November 1998 pp20–21).

The efficacy results were obtained from the following trials:

- Three 12-week pivotal studies (two of knee, and one of hip pain) in about 3,300 osteoarthritis patients, where each study compared celecoxib 50mg twice daily, 100mg twice daily, and 200mg twice daily with naproxen 500mg twice daily and with placebo
- Two 6-week pivotal studies in about 1,300 osteoarthritis patients comparing celecoxib 100mg twice daily and 200mg daily with placebo
- Two 12-week pivotal studies in 2,252 rheumatoid arthritis patients comparing celecoxib 100mg twice daily, 200mg twice daily, and 400mg twice daily with naproxen 500mg twice daily and with placebo
- One 6-month durability study in more than 600 rheumatoid arthritis patients comparing celecoxib 200mg twice daily with slow-release diclofenac 75mg twice daily
- Three 12-hour acute pain studies in more than 700 post-dental surgery patients comparing varying doses of celecoxib (25–400mg) with placebo and either ibuprofen 400mg or naproxen sodium 550mg
- One supporting acute pain study in 255 post-orthopaedic surgery patients comparing celecoxib 100mg twice daily and 200mg twice daily with Lilly's Darvocet N-100 four times daily and with placebo

The trials against naproxen (500mg twice daily) lasted for 12 weeks, and involved 1,149 patients with rheumatoid arthritis and 1,004 patients with osteoarthritis.

In both arthritis conditions, celecoxib (at all three doses of 100mg, 200mg or 400mg twice daily) was better than placebo and similar to naproxen at relieving symptoms (eg joint tenderness, pain and swelling). The upper gastrointestinal safety profile of celecoxib was not significantly different from placebo, but was superior to naproxen. The incidence of endoscopically documented peptic ulcers was 26% for the naproxen group, but only 4% with placebo and with celecoxib 6% at 400mg twice daily, 4% at 200mg twice daily and 6% at 100mg twice daily.

In the comparator trial against diclofenac SR (75mg twice daily), which involved 655 rheumatoid arthritis patients, followed for 24 weeks, celecoxib (200mg twice daily) was as effective in relieving pain and swelling but was associated with significantly fewer gastrointestinal complaints (eg diarrhoea, abdominal pain, dyspepsia). The overall incidence of gastrointestinal complaints during the trial was 36% in the celecoxib group versus 48% in the diclofenac group and withdrawals due to gastrointestinal adverse effects were 6% for celecoxib versus 16% for diclofenac, although withdrawals due to treatment failure were similar (8% versus 7% respectively).

At the end of the study, endoscopy was performed on 430 of the 500 patients who completed and showed significantly fewer gastroduodenal ulcers in the celecoxib group than in the diclofenac group (4% versus 15%). This 24-week endoscopy study was longer than the 3 months recently recommended by the FDA's arthritis advisory committee (*Scrip* 2322, 1 April 1998 p20).

Other Phase III results presented at the ACR meeting showed that celecoxib does not interact with methotrexate or warfarin, two drugs often used in arthritis management. One study measured the effects on platelet aggregation (an event mediated via the COX-1 enzyme), and showed celecoxib to have no effect on platelet aggregation, even at high doses (600mg twice daily), while naproxen at its full therapeutic dose (500mg twice daily) inhibited platelet aggregation by 95%.

4.1.3.2 Celecoxib and its effect on pain

In considering approval of celecoxib, the FDA panel was split on whether clinical trial data supported the additional indication of acute pain management (*Scrip* 2393, 4 December 1998 p18) and did not recommend it for this indication other than in arthritis.

The FDA panellists reviewing the data commented that, despite celecoxib's superiority to placebo, patients were generally still symptomatic. It was noted that following dental surgery, ibuprofen was significantly better than celecoxib at reducing acute pain for the first few hours after taking the drug. It was contended that the post-orthopaedic study failed because the pain measures for both celecoxib and Darvocet were not separated statistically from placebo. This led the FDA to question whether Searle had met the agency's traditional requirement for at least two different types of pain models, that is, single dose, such as in dental pain, and multiple dose, such as in post-operative pain, to be awarded an acute pain management indication. Searle argued that treating the initial flare pain in the early stages of the three 12-week osteoarthritis trials should count as treating acute pain with single doses of celecoxib, in addition to serving as pivotal studies in the treatment of osteoarthritis pain for 3 months. However, the FDA panellists were not convinced.

4.1.3.3 Safety claims for celecoxib

Most of the FDA committee's discussion centred on celecoxib's gastrointestinal safety claims and on Searle's request for establishing a new classification for COX-2 inhibitors, with celecoxib being the first. Avoiding the NSAID class warning about the risk of gastrointestinal ulceration, bleeding and perforation would be a significant marketing advantage for celecoxib. Searle's primary clinical evidence for lower gastrointestinal toxicity was endoscopic examinations of 4,700 patients in five trials in which celecoxib was compared with NSAIDs and placebo (Scrip 2393, 4 December 1998 p18). For the osteoarthritis and rheumatoid arthritis pivotal trials, the company reported a 25% incidence of ulcers in patients who received naproxen, compared with approximately 4% for patients in the other arms of the study. It was stated that the incidence of ulcers with celecoxib was not statistically different from placebo, and that there were no differences across the celecoxib doses. The ulcer incidence was also reported to be much lower with celecoxib than with ibuprofen, and 4% of patients in the 6-month rheumatoid arthritis study, who received celecoxib, developed ulcers, compared with 15% who received diclofenac.

The FDA said that a second study comparing celecoxib with diclofenac found no statistical difference in ulcer rates at the time points studied. The FDA asked the panel what comparisons between celecoxib and NSAIDs, if any, should be allowed in the labelling, considering that only two of the three NSAIDs studied had demonstrated consistent statistical superiority for the COX-2 inhibitor. Several panellists argued that only clinical data, rather than surrogate endoscopic evidence, should be weighed in comparing gastrointestinal toxicities, since these small, localised ulcers may have no relation to the serious upper gastrointestinal complications that lead to an estimated 100,000 hospitalisations and 10,000–20,000 deaths each year in the US.

The company presented clinical data from North American trials showing the incidence of gastrointestinal events was nearly 30% higher for NSAIDs than for celecoxib. It was also pointed out that there was no statistical difference between the incidence of gastrointestinal-related patient withdrawals for celecoxib compared with placebo, whereas the incidence was statistically greater for NSAIDs. However the FDA said that the studies had not been designed to compare clinically significant upper gastrointestinal events. It was pointed out that the data from the submission were not adequate to give an annual incidence rate or statistical information because the studies were of short duration.

The committee declined to endorse Searle's view that celecoxib is the first of a new class of COX inhibitors that are less toxic to the gastrointestinal tract than NSAIDs. Nevertheless, the panel did agree that celecoxib itself has potentially less gastrointestinal toxicity than other NSAIDs (*Scrip* 2393, 4 December 1998 p18). This means that celecoxib carries many of the same warnings as the older NSAIDs, including the potential for renal damage, but unlike other NSAIDs, the celecoxib label states that the drug causes fewer endoscopically diagnosed ulcers and that it does not inhibit platelet aggregation.

The cautionary approach is supported by the fact that the use of the drug has been associated with 10 deaths since its launch in mid-January. However, no direct causality has been found between the deaths and the use of celecoxib. According to Searle, five of the deaths were cardiovascular related, one was involved in hepatic failure, one was a case where the physician specifically stated that there was no relationship to celecoxib, one involved a patient who had an aortic abdominal aneurysm (but was only on the drug for 3 days) and two cases involved elderly patients who experienced gastrointestinal bleeding. They were 77 and

88 years old respectively, had other illnesses and were taking multiple medications which could be linked to gastrointestinal events (*Scrip* 2431, 23 April 1999, p24).

4.1.4 Rofecoxib

The US FDA's arthritis advisory committee has recommended approval of Merck's COX-2 inhibitor, rofecoxib, for the treatment of osteoarthritis and acute pain. Phase III trials in rheumatoid arthritis are currently underway. As with celecoxib, the panel agreed that the labelling for rofecoxib should carry the same warning of gastrointestinal toxicity currently required for all NSAIDs (*Scrip* 2431, 23 April 1999 p18).

In common with celecoxib, rofecoxib is highly specific for the COX-2 enzyme, but does not inhibit COX-1 *in vivo* at therapeutic doses and beyond (*Scrip* 2391, 27 November 1998 p18).

4.1.4.1 Clinical trials

Data are available from studies with more than 10,000 patients, including nine Phase II/III studies in osteoarthritis (four of which are ongoing) and nine Phase II/III studies in acute pain (*Scrip* 2431, 23 April 1999 p18). Results presented at the ACR meeting in San Diego, US (November 1998) were from two Phase III efficacy studies for osteoarthritis, and a pilot Phase II efficacy study for rheumatoid arthritis (*Scrip* 2391, 27 November 1998 p18; *Scrip* 2390, 25 November 1998 p20).

The osteoarthritis studies showed that rofecoxib (at doses of 12.5mg or 25mg once daily) had efficacy comparable to that of the maximum dose of diclofenac (50mg three times daily) and ibuprofen (800mg three times daily). The ibuprofen comparator study was short term, lasting 6 weeks and involving 736 patients, and showed relief from pain and inflammation at 2, 4 and 6 weeks that was comparable in both drug groups, and significantly greater than in the placebo group. The diclofenac comparator study was long term, lasting a year and involving 784 patients, and showed that the treatment effect was maintained.

In both studies, rofecoxib was well tolerated. Side effects such as upper respiratory infection, diarrhoea, nausea and headache were reported with a relatively low incidence and were similar to placebo.

Treatment with the comparator drugs was also generally well tolerated but among the diclofenac patients more discontinuations due to adverse experiences were seen because of abnormal liver tests. The incidence of mild fluid retention was similar across all treatment groups and the incidence of thromboembolic cardiovascular experiences was low (less than 1%) and similar between rofecoxib, diclofenac and ibuprofen.

The second osteoarthritis study was a 6-week study which focused on quality of life (comparing rofecoxib with placebo). It found no differences in factors relating to general health perceptions. Patients on the drug reported significant improvements in physical functioning compared with those on placebo, eg decreased bodily pain and an improved ability to perform everyday activities such as climbing the stairs. This perception of improved physical health resulted directly in a significant improvement in their mental well-being, with patients saying they had more energy, less difficulty working and fewer emotional problems.

The rheumatoid arthritis study was a pilot trial with 133 patients which compared rofecoxib with placebo over a 6-week period. Twice as many patients on the drug as on placebo showed

an improvement in rheumatoid arthritis symptoms such as pain, morning stiffness, joint tenderness and disability. Larger studies in rheumatoid arthritis are now underway.

Rofecoxib has shown gastrointestinal safety similar to placebo in an endoscopy study, even at doses ten times higher than those currently being used in Phase III clinical trials. Similar endoscopy studies over the entire length of the gastrointestinal tract suggested to the company that rofecoxib induces less damage than ibuprofen and indomethacin. Five dose-ranging Phase II studies showed that the once-daily drug relieved the symptoms of osteoarthritis and rheumatoid arthritis, was as effective as naproxen and ibuprofen against pain following dental surgery and was more effective than ibuprofen for menstrual cramps and pain (*Scrip* 2335, 15 May 1998 p27).

The results of two studies which support these findings (see *Scrip* 2380, 21 October 1998 p26) evaluated gastrointestinal blood loss and gastrointestinal permeability. Gastrointestinal permeability is believed to be an indicator of gastrointestinal toxicity, particularly low-grade inflammation, bleeding and intestinal protein loss.

In the first study, 67 healthy volunteers were randomised to either 25mg or 50mg of rofecoxib once a day, 800mg of ibuprofen three times a day, or placebo, for 4 weeks. Volunteers on both doses of rofecoxib had no significant differences in blood loss compared with those on placebo. However, volunteers on ibuprofen had twice as much blood loss as those on either rofecoxib or placebo.

In the second study, 39 volunteers were randomised to 25mg or 50mg of rofecoxib once a day, 50mg of indomethacin three times a day or placebo for 7 days. Gastrointestinal permeability in volunteers on rofecoxib was not significantly different from that of those on placebo but those on indomethacin had significant increases of up to 58% permeability.

Two 6-month safety studies, recently reported by Merck, which evaluated 1,427 osteoarthritis patients, showed that rofecoxib caused less gastrointestinal toxicity than ibuprofen (reported in *Scrip* 2396, 16 December 1998 p20). These data are the first to show a reduction in serious gastrointestinal side effects with rofecoxib compared with other NSAIDs. The cumulative rate of ulcers for once-daily rofecoxib (25mg and 50mg) was similar to that for placebo and significantly less than for ibuprofen (800mg three times daily). Data for weeks 12 and 24 of the trials are presented in Table 4.2.

Table 4.2: Cumulative rate of ulcers for once-daily rofecoxib compared with ibuprofen and placebo

	Week 12 (% ulcers)	Week 24 (% ulcers)
Placebo	7.3	*
Rofecoxib 25mg	4.7	9.7
Rofecoxib 50mg	8.1	13.5
Ibuprofen	28.5	46.4

Source: Scrip 2396, 16 December 1998 p20.
*Note: *The placebo arm was discontinued at week 16.*

Effects on renal function were reported to be similar to those seen with other drugs, including the NSAIDs known to act on similar biochemical targets.

The FDA advisory committee that approved the drug were concerned about the potential of rofecoxib for dosage creep with a resultant increase in adverse events, including hypertension and peripheral oedema. This could be important in the treatment of rheumatoid arthritis where the required dose is likely to be more than 25mg a day (*Scrip* 2431 23 April 1999 p18).

4.1.4.2 Competition with celecoxib

Although celecoxib reached the market first, rofecoxib is expected to have a competitive advantage in terms of pain indication because Merck has conducted longer pain studies (*Scrip* 2396, 16 December 1998 p13). However, it is expected that the FDA will require the rofecoxib data sheet to carry the standard NSAID class label warning about the risk of gastrointestinal ulceration, although with slight modifications.

The indication approved by the FDA for celecoxib is broader than for rofecoxib, covering treatment of acute or chronic signs and symptoms of osteoarthritis and rheumatoid arthritis and the management of pain. Merck plans to file for the treatment of osteoarthritis and management of pain, but is still studying the drug in rheumatoid arthritis. There is a difference in administration which may benefit the marketing of rofecoxib, because although both are oral tablets, rofecoxib is a once daily medication while celecoxib needs to be taken twice daily.

Rofecoxib has been approved in Mexico and in the US, where it is expected to be available to pharmacists from mid-June 1999.

Searle and Merck are exploring the potential of their respective COX-2 inhibitors, celecoxib and rofecoxib in the treatment of colon cancer and Alzheimer's disease (*Scrip* 2434/2435 5/7 May 1999 p29), thus broadening the potential applications of these drugs. There have been suggestions that the anti-inflammatory effects of NSAIDs may be beneficial in both conditions, but until now, their gastrointestinal toxicity has precluded further investigation. The COX-2 inhibitors, with their better gastrointestinal profile, allow clinical testing of these diseases.

Searle, in conjunction with Pfizer, has begun a Phase III study of celecoxib for colon cancer, following encouraging results in the treatment of familial adenomatous polyposis, a condition which is associated with colon cancer. The two companies expect to file an NDA later this year for the reduction of colon polyps in patients with a genetic predisposition to the disease. Merck is planning to develop rofecoxib for the prevention of colon polyps and tumours. It expects to begin Phase II trials later this year.

Merck already has two Phase II studies of rofecoxib underway in Alzheimer's The first is investigating whether it can prevent or delay the onset of the disease in at-risk patients (those with mild cognitive impairment). The second is evaluating whether rofecoxib can slow the progression of the symptoms of Alzheimer's in patients diagnosed with the disease. Celecoxib is also being investigated for the treatment of Alzheimer's in a study that began 2 years ago.

Other indications being studied are sporadic adenomatous polyposis, bladder cancer, actinic keratosis and Barrett's oesophagus.

4.2 Anti-TNF agents

The role of TNF-α in the inflammatory process and its role in the pathogenesis of rheumatoid arthritis was discussed in Chapters 1 and 2 respectively. It is discussed here with respect to progress in the development of novel anti-TNF agents as a new treatment option.

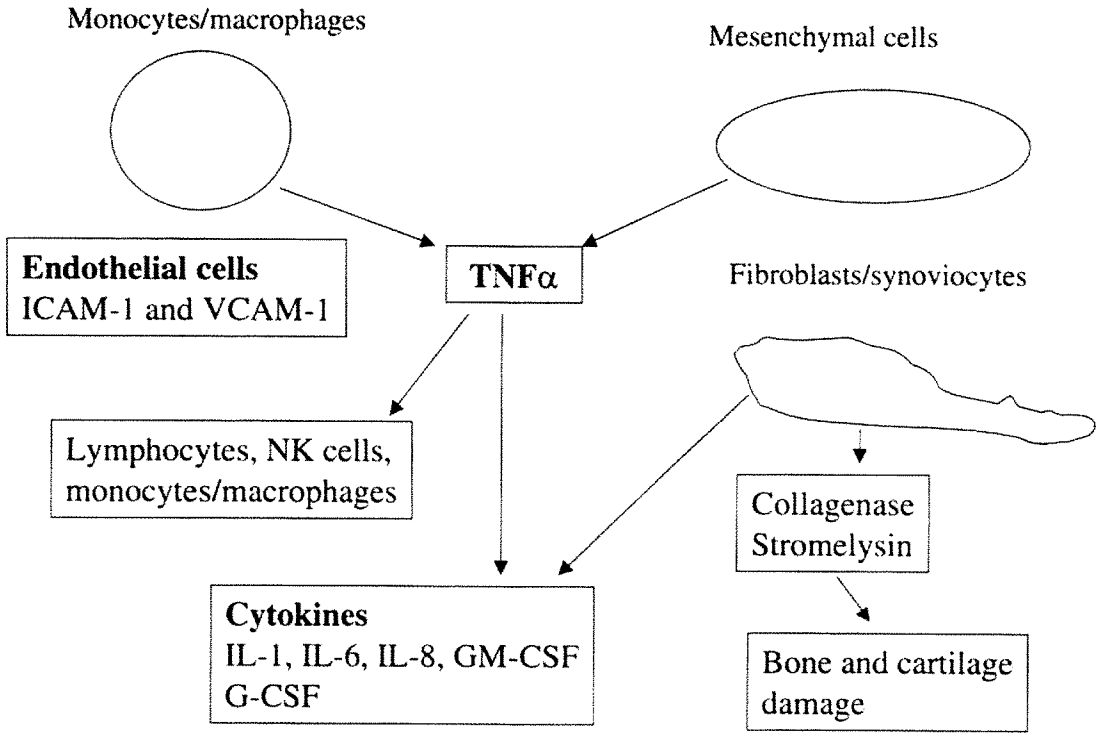
In healthy individuals, TNF-α is secreted in response to an infection in order to ward off bacteria or viruses. However, in patients with rheumatoid arthritis, it is found at high levels in the synovial fluid surrounding the affected joints and is involved in the cascade of inflammatory events that eventually destroy joint tissue. The possibility that TNF-α might be implicated in the pathogenesis of rheumatoid arthritis arose from a number of observations *in vitro* (Brennan & Feldmann, 1992; Arend & Dayer, 1995). TNF-α is produced primarily by the synovial macrophages. It is able to induce the proliferation of synovial cells (the fibroblast-like cells that line the joint) and to increase their production of PGs and other cytokines (Nawroth *et al*, 1986; Brennan *et al*, 1989). It also stimulates the production of collagenases and metalloproteinases (enzymes that damage bone and cartilage) from neutrophils, fibroblasts and chondrocytes (Dayer *et al*, 1985; Ahmadzadeh *et al*, 1990; Alvaro-Gracia *et al*, 1990; MacNaul *et al*, 1992; Shingu *et al*, 1993). It stimulates fibroblast growth (Vilcek *et al*, 1986) and induces resorption of bone and cartilage (Bertolini *et al*, 1986).

In summary, TNF-α:

- Prompts cells in the affected joint (neutrophils, fibroblasts and chondrocytes) to produce enzymes (collagenases and metalloproteinases) that damage bone and cartilage
- Triggers the release of other substances (PGs) that contribute to joint injury and inflammation
- Directs the production of other cytokines, thereby perpetuating the cascade of inflammatory events (IL-1 and GM-CSF)

These effects are summarised in Figure 4.2.

Figure 4.2: The biological effects of TNF-α



Source: Choy et al. Monoclonal antibody therapy in rheumatoid arthritis. British Journal of Rheumatology 1998; 37, 484–490. Published with the permission of the authors and Oxford University Press.
Note: VCAM-1=vascular adhesion molecule-1.

TNF-α has therefore become a therapeutic target for developing drugs for rheumatoid arthritis. Treatments that inhibit its activity are the first biological agents to represent a major therapeutic advance in the treatment of the disease. The discovery of two soluble TNF receptors, p55 TNFR and p75 TNFR has been exploited for therapeutic purposes by using DNA technology for the construction of dimeric TNFR-Fc immunoglobulin fusion proteins as TNF inhibitors.

The new anti-TNF drugs act like sponges to mop up the high concentrations of TNF found in affected joints. By doing so, they reduce the inflammation – the signs and symptoms of disease. There is hope that they will also delay disease progression, although this has yet to be shown.

4.2.1 Launched and emerging anti-TNF agents

Immunex's Enbrel (etanercept) has recently been launched for rheumatoid arthritis and there are also two more products targeting TNF coming through the R&D pipelines. These are Centocor's Remicade (infliximab), which is in Phase III clinical trials, and Knoll/CAT's D2E7, which is in Phase II studies. The three products represent a new approach to the treatment of rheumatoid arthritis and were described as a breakthrough at the November 1998 meeting of the ACR in San Diego, California (*Scrip* 2389, 20 November 1998 pp24–25).

Although all three of these anti-TNF drugs act broadly in the same manner, by mopping up excess TNF in the affected joints of rheumatoid arthritis patients, they achieve that effect by slightly different mechanisms. They also differ in structure and mode of administration.

Etanercept is a TNF receptor p75 fusion protein which competitively inhibits the binding of TNF to TNF receptor sites. It consists of part of an antibody (IgG1 isotype) attached to a soluble TNF receptor. It is not antigenic but has a shorter half-life than a true antibody. It neutralises both forms of TNF, namely, TNF-α and TNF-β.

In contrast, infliximab and D2E7 are both monoclonal antibodies (IgG1 isotypes) specifically targeting TNF-α. Infliximab is a chimaeric product (about two-thirds human and one-third mouse), whereas D2E7 is fully human. These differences are thought to account for differences in antigenicity. Infliximab doses are spaced at long intervals and are given together with methotrexate to reduce the response that the body mounts to the product, whereas D2E7 is administered on its own and has been given chronically without tolerance developing.

All three products, as proteins, have to be given parenterally, but the route varies. Etanercept and D2E7 can be injected subcutaneously, etanercept twice weekly, D2E7 once a week. Both of these products can be self-administered by the patient at home, although D2E7 has also been given by intravenous bolus, which would necessitate a clinic visit. On the other hand, infliximab is given every 4–8 weeks but must be infused, thus requiring a visit to the clinic.

Although the anti-TNF drugs have been hailed as a breakthrough in the treatment of rheumatoid arthritis, their potential for halting this crippling disease has yet to be demonstrated. The data so far focus on disease activity, for which the drugs are effective, but whether they have an effect on disease progression has yet to be determined. Theoretically, by blocking TNF at an early stage of the inflammatory cascade, they should halt the destruction that leads to joint erosion. The specificity of this action should make them better tolerated than the DMARDs currently in use.

4.2.1.1 Etanercept

Etanercept is a soluble recombinant human p75 TNF receptor and human IgG1 Fc portion fusion protein. It is composed of two TNF-binding domains derived from the p75 TNF-α receptor fused with the Fc fragment of human immunoglobulin (Moreland *et al*, 1997a). It has just been launched in the US (*Scrip* 2385, 6 November 1998 p14), where it is co-promoted by Immunex and Wyeth-Ayerst, and is now awaiting registration in the EC, where it will be marketed by Wyeth-Ayerst. In the US, it is licensed for moderate to severe rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. The US labelling for etanercept, the first of the anti-TNF products, suggests that at present, it is considered a third-line option, to be used after NSAIDs such as ibuprofen and diclofenac and after DMARDs such as sulphasalazine and methotrexate, and Hoechst Marion Roussel's newly launched leflunomide.

Although etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone, it is not yet recommended for use in combination with other DMARDs. This is because it has so far only been studied with methotrexate. Glucocorticoids, salicylates, NSAIDs or analgesics may be continued during treatment with etanercept.

The market analysts, CIBC Oppenheimer, have argued that, as methotrexate is the gold standard for severe rheumatoid arthritis, the safety of etanercept in combination with methotrexate needs to be established in order to extend etanercept's use. Since it is currently only available to patients who have failed therapy with other agents (about 500,000 patients in the US), it needs to be extended to all patients receiving treatment (an additional 700,000 patients). These are mostly being treated by primary care physicians (*Scrip* 2360, 12 August 1998 p20).

. . . clinical trials

Approval of the drug was based on data from 745 patients who took etanercept as part of three previously reported randomised, placebo-controlled clinical trials (*Scrip* 2372, 23 September 1998 p25). In all, 1,381 patients participated in the three trials, 1,039 of whom received etanercept.

The most recent of the three studies was designed to confirm the benefit of etanercept therapy of longer duration and simplified dosing in patients with rheumatoid arthritis (Moreland *et al*, 1999). It was a randomised double-blind, placebo-controlled trial with blinded joint assessors and involved 234 patients with active rheumatoid arthritis who had not responded to DMARDs. The treatment was twice-weekly subcutaneous injection of either 10mg or 25mg etanercept or placebo for 6 months. Etanercept significantly reduced disease activity in a dose-related manner. At 3 months, 62% of rheumatoid arthritis patients who received 25mg etanercept and 45% who received 10mg, showed a 20% improvement and patients on placebo had a 23% improvement. Disease improvement was measured as the ACR20 response which represents a 20% reduction in a number of parameters including number of swollen and tender joint counts, assessments made by physicians and patients, as well as laboratory markers of inflammation and pain. Secondary endpoints are the ACR50 and ACR70 responses, representing 50% and 70% reductions respectively. These criteria have been described by Ramey *et al* (1996b).

After 6 months, 59% of patients on 25mg of etanercept and 51% on 10mg showed a 20% improvement. Patients on placebo had an 11% improvement after 6 months. Similarly, in response to a health assessment questionnaire, 44% of patients receiving 25mg of etanercept and 27% of those receiving 10mg, reported significant improvement in physical function. Thirty percent of patients on 25mg and 25% on 10mg said they experienced increased vitality. These results are summarised in Table 4.3.

Table 4.3: Summary of results of a Phase III clinical trial with etanercept

	10mg etanercept (% response)	**25mg etanercept (% response)**	**Placebo (% response)**
ACR20 (at 3 months)	20	62	23
ACR20 (at 6 months)	51	59	11
Improved physical function	27	44	Not reported
Increased vitality	25	30	Not reported

Source: Scrip *2372, 23 September 1998 p25.*

Immunex claims that the results clearly show a dose-related response. Patients receiving the lower dose of etanercept responded better than those on placebo. The most common drug-related side effect was reported to be injection site reaction. Most reactions were mild and

occurred within the first 4 weeks of treatment and more than half the patients had no such reactions. More serious were 22 cases of upper respiratory tract infection. The infections were the same as those seen in other rheumatoid arthritis patients. One 54-year old woman with rheumatoid arthritis who received etanercept died of severe sepsis. Whether the death was caused by the product or the seriousness of her disease is unclear. Seven cases of cancer developed among the 745 patients who received etanercept, a rate similar to that of the general population.

At the ACR meeting (San Diego, November 1998), new data were presented from an ongoing 2-year open-label safety study of etanercept, which, according to Immunex and Wyeth-Ayerst, confirmed its good tolerability. Results were presented for 51 patients who had completed more than 2 years of treatment. A further 32 patients are continuing, but have not reached this time point yet, and 22 of the original 105 have dropped out or been lost to follow-up. Efficacy was assessed on the Paulus response composite score (which requires a greater than 20% improvement in four of six parameters such as tenderness and swelling of the joints, morning stiffness, etc). Of the 51 patients completing 2 years of treatment, 88% had a Paulus response of 20% (meaning at least a 20% improvement in clinical parameters), 65% had a response of 50%, and 39% experienced a response of 70%. The companies observed that adverse event rates were consistent with other etanercept studies, and that there was no increase in adverse drug reactions (ADRs) with prolonged use. The most frequently reported ADRs were mild to moderate injection site reactions.

Patients treated with methotrexate often improve but continue to have active disease. In March 1998, Immunex reported positive results from a US trial comparing methotrexate alone with etanercept plus methotrexate in the treatment of persistently active rheumatoid arthritis (*Scrip* 2360, 12 August 1998 p20). This Phase II/III study, now published by Weinblatt *et al* (1999), involved 89 patients treated in a 2:1 randomisation with 25mg of etanercept or placebo twice a week with methotrexate. The primary measure of clinical response was the ACR20 response. Data at 24 weeks showed that 71% patients receiving etanercept with methotrexate and 27% of those receiving placebo plus methotrexate achieved the ACR20 criteria. Thirty nine percent of the patients receiving etanercept plus methotrexate and 3% of those receiving placebo plus methotrexate met the ACR50 criteria. Overall, patients receiving etanercept plus methotrexate had a significant decrease in disease activity and an increase in functional ability, compared with those treated with methotrexate alone. There was no significant difference in the incidence of side effects between the two treatment groups.

Immunex is collecting X-ray data on disease progression from an ongoing study of etanercept in 600 patients with early rheumatoid arthritis and intends to file a supplemental US NDA on the basis of these results, which are expected in the first half of 1999 (*Scrip* 2370, 16 September 1998 p22).

. . . use of etanercept in juvenile rheumatoid arthritis

Immunex has filed a supplemental biologics licence application with the US FDA to obtain marketing approval for the use of etanercept in children and teenagers (aged 4–17 years) with moderately to severely active polyarticular course juvenile rheumatoid arthritis (*Scrip* 2392, 2 December 1998, p27). The agency has already notified the company that this indication will qualify for orphan drug status in the event that the supplemental application is approved. About 50,000 children in the US have juvenile rheumatoid arthritis.

. . . cost

As expected, the cost of etanercept is well above that of other rheumatoid arthritis therapies. At an average wholesale price of $110 per vial, and with a dosing regimen of one 25mg subcutaneous injection twice weekly, the drug will cost patients $11,440 plus a pharmacy mark-up annually. It remains unclear to what extent managed care insurers will cover the drug. Since the price of etanercept is expected to be very high patients will probably require private insurance to afford it.

. . . market potential

Assuming a 5% market penetration of an estimated 600,000 rheumatoid arthritis patients in the US, who have failed on methotrexate, an annual pricing in the $10,000 range would generate $300 million. CIBC Oppenheimer has estimated sales of etanercept in 1999 at $146 million and in 2000 at $275 million (*Scrip* 2384, 4 November 1998 p10). Further information is given in Chapter 6.

. . . competition

Etanercept will compete with Hoechst Marion Roussel's oral isoxazole, leflunomide, which was launched in the US at the end of September 1998 for reducing the signs and symptoms of the disease and retarding structural damage; this is the first oral treatment approved specifically for slowing progression of rheumatoid arthritis (*Scrip* 2370, 16 September 1998 p22). Although leflunomide is a non-specific DMARD, it has a claim for delaying structural damage backed by X-ray evidence, is taken orally and costs around $3,000 annually. Etanercept on the other hand, is administered by subcutaneous injection twice a week, and is expensive, costing more than $11,000 annually.

. . . safety

The warnings section of the data sheet notes that etanercept should be discontinued if a patient develops a serious infection. In a study of 49 patients with rheumatoid arthritis treated with etanercept, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with etanercept on the development and course of malignancies and infections is not fully understood. The safety and efficacy of etanercept in patients with immunosuppression or chronic infections has not been evaluated.

. . . new studies

Immunex has commenced a study of etanercept in early rheumatoid arthritis in about 600 patients. Results are expected in the first half of 1999.

4.2.1.2 Infliximab

Infliximab is a mouse MAb against TNF-α grafted on to a human immunoglobulin constant (Fc) region. The antibody binds to TNF-α and neutralises its activity. It has a different mechanism of action from Immunex' etanercept. Although both are anti-TNF agents, etanercept, as indicated above, is composed of two soluble TNF receptors connected to a fixed chain of an antibody and works by mopping up excess TNF in the bloodstream.

Infliximab, on the other hand, is a chimaeric antibody and binds both to TNF in the bloodstream and to cell-bound TNF.

Infliximab was launched in the US, in October 1998 for the treatment of Crohn's disease (see below). The product is expected to be available in Europe in the first half of 1999 (*Scrip* 2378, 14 October 1998 p20) where it will be marketed by Schering-Plough. A regulatory submission with the FDA for the use of infliximab for the treatment of rheumatoid arthritis is planned for January 1999 with a possible market launch by the end of 1999. The company intends to seek approval for rheumatoid arthritis initially in refractory patients (*Scrip* 2378, 14 October 1998 p20).

. . . clinical trials

The basis of the rheumatoid arthritis submission was data from the 30-week Phase III ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) study, reported in *Scrip* 2389, 20 November 1998 pp24–25, and presented at the ACR meeting in San Diego, November 1998. The study spanned North America and Europe and involved 428 patients with progressive or advanced rheumatoid arthritis who were particularly difficult to manage. All patients had active rheumatoid arthritis (usually for more than 3 years), despite treatment with methotrexate. They were treated with methotrexate together with either infliximab, 3mg/kg or 10mg/kg, infused every 4 or 8 weeks, or placebo.

Consistent benefits were seen in patients receiving infliximab compared with placebo, with significant reductions in the signs and symptoms of rheumatoid arthritis. The primary endpoint of the study was the ACR20 response. Secondary endpoints were ACR50 and ACR70 responses.

Significant differences were seen in all three measures; an ACR20 response was seen in 52% of infliximab patients compared with 20% in placebo treated patients, an ACR50 response in 28% compared with 5%, and an ACR70 response in 12% compared with 0%.

Significant differences were seen in many of the disease parameters. For example, swollen joints were reduced by 57% in patients on infliximab compared with 20% on placebo, and tender joint counts were reduced by 61% compared with 26% respectively. The most common adverse events included respiratory tract infection, headache, nausea, sinusitis, rash and cough. Similar rates were seen in infliximab and placebo groups for serious adverse events (11% compared with 16%), serious infections (4% compared with 6%) and infusion reactions (5% compared with 2%).

The results are particularly noteworthy because all patients in the trial had advanced disease. The majority of patients responding to infliximab did so within 2 weeks of the first infusion.

The company noted that the 3mg/kg infusion every 8 weeks gave optimum results. The ATTRACT trial will continue for another 18 months to evaluate long-term use of the drug and also to determine whether therapy with infliximab will ultimately lead to prevention of structural damage and improvement in functional ability.

. . . neutralising antibodies

Since infliximab is a chimaeric MAb to the TNF-α molecule, its long-term use in rheumatoid arthritis may be limited by neutralising antibodies. The FDA has shown concern about the

appearance of serious adverse effects in a small group of Crohn's disease patients treated in early clinical trials with infliximab and then re-treated 2–4 years later. The reactions appeared to be related to development of an immune response to infliximab. As a result, at the request of the FDA, Centocor has issued a 'Dear Doctor' letter in the US regarding a potential immune reaction following re-treatment with infliximab after an extensive period without treatment (*Scrip* 2390, 25 November 1998 pp20–21).

However, Centocor stressed that in an ongoing Phase III study, 340 patients have been re-treated every 4–8 weeks for a period of more than 6 months with a lyophilised formulation of infliximab similar to the currently marketed product. None of these patients has developed a similar set of delayed adverse events. Centocor believes that this is a good indication of how the drug behaves in a re-treatment setting. This trial is scheduled to continue for another 18 months.

Analysts are suggesting that while the data presented so far appear to indicate that re-treatment concerns are not a big issue in rheumatoid arthritis, it is too early to say that the long-term situation may be.

. . . market potential

Hambrecht & Quist analysts forecast that an approval for rheumatoid arthritis for the most severe patients could add $21 million in worldwide sales in 1999 and $158 million in 2000, bringing total infliximab sales to $130 million and $284 million in 1999 and 2000 respectively. Most of the rheumatoid arthritis sales for 1999 and 2000 are expected to be in the US (*Scrip* 2378, 14 October 1998 p20).

. . . infliximab and Crohn's disease

Infliximab has already been launched in the US for the treatment of patients with active Crohn's disease and information is available concerning its safety and side effects which are relevant to rheumatoid arthritis.

Crohn's disease is a serious, chronic inflammatory disease of the small and large intestine, as well as other parts of the digestive tract. Its cause is unknown. The indication includes patients with fistulae. These are painful channels that open between the bowel and the skin, mostly in the perianal area, causing drainage of mucous and/or faecal material (*Scrip* 2378, 14 October 1998 p20). An estimated 200,000 people in the US, and an equal number in Europe, have the disease and between 5,000 and 10,000 new cases per year are reported in the US (*Scrip* 2340, 3 June 1998 p25). About 15–30% of patients have the fistulising form of the disease.

To date, no drug has been approved specifically for Crohn's disease, which is classified as an orphan disease in the US. Corticosteroids, immunosuppressive drugs and antibiotics, particularly metronidazole, are frequently prescribed, and all have significant toxicity. Infliximab is the first new drug for this indication in 30 years.

Data presented to the FDA by Centocor were from two large placebo-controlled trials in Crohn's disease, CO168T16 (or T16) and CO168T20 (or T20) (*Scrip* 2340, 3 June 1998 p25). In study T16, 108 patients who had failed on other treatments were randomised to placebo, or one of three doses of infliximab, formerly known as Avakine, (5mg/kg, 10mg/kg, or 20mg/kg). The primary endpoint was a clinical response at 4 weeks, defined as at least a

70-point decrease in Crohn's Disease Activity Index (CDAI) compared with baseline. (The CDAI is a composite score of signs and symptoms ranging from 0 to 600; patients with CDAI scores over 300 are considered to be in poor condition.) This 70 point decrease was achieved in 17% of placebo patients, 81% of those on the 5mg/kg dose of infliximab (p=0.001), 50% on the 10mg/kg dose (p=0.045) and 64% on the 20mg/kg dose. At the 5mg/kg dose, 48% of patients achieved clinical remission (CDAI<150), compared with 4% of patients on placebo. For all three infliximab-treated groups combined, 65% of the patients demonstrated a clinical response (p=0.001) and 33% achieved clinical remission (p=0.005).

In study T20, 94 patients with draining fistulae were randomised to placebo or infliximab at doses of 5mg/kg or 10mg/kg. Patients were evaluated every 4 weeks until week 18 and responders continued through week 26 for additional evaluation. The primary endpoint was at least a 50% reduction in the number of open fistulae for at least two consecutive evaluation visits. This occurred in 26% of placebo patients, 68% of those on infliximab 5mg/kg (p=0.002), and 56% of those on 10mg/kg (p=0.021). At the 5mg/kg dose, 55% of patients had a complete response (all fistulae closed for two consecutive study visits). For both infliximab groups combined, 62% of patients achieved the primary endpoint (p=0.002), and 46% had a complete response (p=0.001). These findings were said to represent the first time that a statistically significant therapeutic benefit has been demonstrated in the closure of draining fistulae.

It was noted that 12 deaths occurred among the 462 patients who received infliximab in the Centocor trials compared with no deaths among the 61 placebo patients. Three deaths were in the Crohn's trials (one cardiac, one malignancy, and one pulmonary) and nine were in the rheumatoid arthritis trials (four cardiac, three malignancy, two pulmonary). Also, one death occurred in an National Institutes of Health (NIH) AIDS trial. Nine malignancies occurred in infliximab patients compared with none in placebo patients. Serious infections were also more frequent in infliximab patients (15 cases, including five of pneumonia and two of cellulitis) compared with two in placebo patients. There were also more infusion reactions (headache, nausea, dizziness, flushing, chest pain, hypertension and abdominal pain) with infliximab (72 compared with nine with placebo). Four of the infusion reactions among infliximab patients (including three cardiopulmonary reactions in the Crohn's trial) were considered serious. It was suggested that the infusion reactions might be associated with antibodies formed against mouse elements in the infliximab protein. Of 80 patients who developed these antibodies, 36% had an infusion reaction, compared with 11% of the 203 patients who did not form such antibodies.

Two other antibodies were of concern to the FDA because of their association with destructive autoimmune reactions. These were anti-nuclear antibodies (ANA) and antibodies against double-stranded DNA (dsDNA) which are characteristic of systemic lupus erythematosus. Lupus was reported in one patient in the Crohn's trials and one in the rheumatoid arthritis trials. There was an overall net increase in ANA seropositivity in infliximab patients, occurring in 36% of patients at the end of the trials compared with 24% at baseline. No placebo patient became positive to anti-dsDNA antibody, compared with 33 patients who received infliximab and 13 of these remained positive at their last visit. For these antibody formations, there was an association with use of immunosuppressants, which are commonly taken by patients with Crohn's disease and rheumatoid arthritis.

The approved labelling and dosage recommendations allow a patient with fistulae to receive three infliximab infusions. Those with moderate to severe active Crohn's receive a single

infusion to start, but there is nothing to stop a physician from re-treating these patients if their disease becomes active again.

The US list price of infliximab to wholesalers is $450 per vial, and the average Crohn's patient will require three to four vials per infusion, at a cost of $1,350–$1,800 plus a pharmacy mark-up. Patients with fistulae will require three infusions (at weeks 0, 2 and 6), while patients without fistulae are likely to require one infusion. The recommended dosage for patients with non-fistulising moderate to severe, active Crohn's disease is a single infusion of 5mg/kg of infliximab. The dosage for patients with fistulising disease is an initial dose of 5mg/kg followed by additional doses of 5mg/kg at 2 and 6 weeks after the first infusion. The data sheet states that the safety and efficacy of more than three doses of infliximab is unknown, so Centocor will need additional data to support its use other than for the short term. The product is expected to make a significant difference to the lives of people with Crohn's disease because it can close fistulae.

The company predicts 1999 worldwide sales of about $120–$140 million, most of which will be in the US, with a launch in Europe expected in the second half of 1999.

Some analysts feel that infliximab's indications are somewhat narrow. It is approved for reducing signs and symptoms in patients with moderately to severely active Crohn's disease who have an inadequate response to conventional therapy, and for reducing the number of draining enterocutaneous fistulae in patients with fistulising Crohn's disease.

Given the narrow indications, analysts at CIBC Oppenheimer expect peak US sales of infliximab to be around $100 million per year for Crohn's disease. This is based on an estimated 70,000 patients in the US diagnosed at any one time with active moderate to severe Crohn's. They predict year-end US sales of $10 million in 1998, and $60 million for 1999.

Hambrecht & Quist analysts predict US sales of $28 million in 1998 (representing a 12% penetration into the market for patients with fistulae and a 6% penetration into the moderate to severe population). By 1999, they forecast worldwide sales of $110 million ($102 million of these in the US), which includes about $20 million in potential revenues from off-label use in rheumatoid arthritis. They predict sales to rise to $125 million by 2000. In Europe, they forecast, sales will be approximately 20% of US sales.

. . . other markets

In 2000 Centocor plans to bring infliximab into clinical trials for psoriasis, asthma and ulcerative colitis and other forms of IBD.

4.2.1.3 D2E7

Further back in development is D2E7, originally made by Cambridge Antibody Technology in the UK, but now being developed and commercialised by Knoll AG (BASF Pharma). D2E7 is in Phase II trials for rheumatoid arthritis in the US and Europe, and is also under investigation for sepsis and IBD.

Data from Phase II studies involving a total of 140 patients with active rheumatoid arthritis presented at the ACR meeting in San Diego in November 1998, showed that D2E7 was safe and effective in reducing disease activity when administered either intravenously or subcutaneously (*Scrip* 2389, 20 November 1998 pp24–25). Both routes of administration

were equally effective. Chronic treatment was given either by subcutaneous injection once a week for a period of 3 months, or by an intravenous bolus injection once every 2 weeks (or at longer intervals, depending on response) for a period of 6 months. The minimum effective dose was 0.5mg/kg.

In these chronic treatment open-label studies, up to 80% of patients achieved and sustained a 'clinically significant good response'. The response to treatment was measured on the European Disease Activity Score (DAS), which includes joint counts, patient pain scores and laboratory measures. A 'good response' to treatment was defined as a fall below 2.4 on the DAS (which is broadly similar to the US ACR20 response).

The patients taking part in the studies had a mean DAS of 5.4 before treatment, with an average duration of disease of 10–11 years, and had already tried three to four different DMARDs (but underwent a wash-out period before starting the trial). In addition, a 60% reduction in the number of swollen and tender joint counts was observed.

In the single dosing study with an intravenous bolus injection, a response to treatment was seen within 24 hours. This contrasts with the weeks, sometimes months, that elapse before responses to DMARDs are observed.

Peak sales potential of D2E7 is estimated at $335–447 million (DM 600–800 million) (*Scrip* 2380, 21 October 1998 p10).

4.2.2 Limitations of anti-TNF-α drugs

In general, anti-TNF therapeutics are well tolerated during and immediately after administration. However, TNF-α has evolved to perform specific functions and blocking its action in arthritic joints could have unwanted side effects. For instance, opportunistic infections and increased malignancies are possibilities despite the fact that there is as yet no substantial evidence for this. Also of concern is the induction of anti-nuclear and anti-DNA antibodies and in some cases, systemic lupus erythematosus by these drugs (see Section 4.2.1.2 on Crohn's disease). Further to this, these drugs must be administered parenterally which is a disadvantage for long-term treatment. It is most likely that these drugs will be used to control very aggressive disease in conjunction with conventional drugs (Firestein & Zvaifler, 1997). With respect to our understanding of the pathogenesis of rheumatoid arthritis and developing new drugs, TNF-α can be considered an important new therapeutic target for the new millennium.

4.3 New DMARDs

4.3.1 Leflunomide

Hoechst Marion Roussel's oral DMARD, leflunomide, has been launched in the US, its first market. Leflunomide is the first drug to be indicated for delaying structural damage in rheumatoid arthritis, and is the first DMARD to be approved for more than a decade (*Scrip* 2387, 13 November 1998 p19). It was cleared by the FDA in September 1998 (*Scrip* 2370, 16 September 1998 p22), having been unanimously recommended for approval by the FDA's arthritis advisory committee in August (*Scrip* 2360, 12 August 1998 p19). The product is awaiting registration in Europe, where a centralised filing was made in February 1998. First European approvals are expected around mid-1999.

Leflunomide has a new mechanism of action for a DMARD; it acts selectively on lymphocytes, and interferes with their ability to produce the adverse response that ultimately leads to joint damage. It is a pro-drug; its active metabolite (A77 1726) is a reversible inhibitor of the enzyme dihydroorotate dehydrogenase (DHODH), which is involved in *de novo* pyrimidine synthesis and is consequently essential for RNA synthesis. At low levels of ribonucleotides, p53, a 'sensor' molecule is activated and prevents progression through the cell cycle, arresting the cells at the G_1 phase. This leads to inhibition of lymphocyte proliferation, a key event in the pathogenesis of rheumatoid arthritis. Cells such as activated T-cells that predominantly synthesise pyrimidines by the *de novo* pathway appear to be especially sensitive to the effect of leflunomide. Further details can be obtained from a paper by Fox (1998).

4.3.1.1 Clinical trials

Approval of the drug was based on the results of three randomised, Phase III, pivotal trials in which a loading dose of 100mg/day of leflunomide was given to patients at the beginning of their treatment, followed by a maintenance dose of 20mg/day (all trials were reported in *Scrip* 2360, 12 August 1998 p19). Trial 301US, conducted in the US and Canada, compared 182 patients on leflunomide with 118 patients on placebo and 182 patients on 7.5–15mg of methotrexate per week for 12 months (reported by Weaver *et al* at the ACR meeting in San Diego, November 1998). Patients who completed 12 months are being followed, still blinded, for 24 months. Trial 301MN, conducted in Europe, South Africa and Australia, compared 133 patients on leflunomide with 92 patients on placebo and 133 patients on 0.5–2g of sulphasalazine per day for 6 months, after which patients on placebo were allowed to switch to sulphasalazine (published by Smolen *et al*, 1999). Active treatment groups were followed blinded, for 12 months. Trial 302MN, conducted in Europe and South Africa, compared 501 patients on leflunomide with 498 patients on 7.5–15mg of methotrexate per week for 12 months. The primary outcome measure was the success rate in achieving ACR response criteria. In study 301US, 41% of the leflunomide arm, 19% of those on placebo, and 35% on methotrexate achieved ACR success (completed 12 months of treatment and ACR responder at endpoint). In study 301MN, this was achieved by 49% of leflunomide patients, 29% on placebo, and 45% on sulphasalazine. However, in study 302MN, only 43% of leflunomide patients compared with 57% on methotrexate achieved ACR success.

In trial 301US, the effects of therapy were measured on a Health Assessment Questionnaire which included questions on everyday activities such as dressing, walking, eating etc. Patients on leflunomide had, statistically, significantly better physical function compared with those on placebo and methotrexate (35% versus 2% versus 20% respectively) over the whole 12-month period. In the same study, X-ray analysis of bone erosion and joint space in the hands and feet showed that patients on leflunomide had significantly less disease progression than those on placebo and also less than those on methotrexate (0.5% versus 2.2% versus 0.9% respectively). The lead investigator, Dr Arthur Weaver, medical director of the Arthritis Centre of Nebraska said that these data showed that leflunomide has the capacity to interfere with the disease process and slow the progression of disability. He pointed out that it would allow many rheumatoid arthritis patients to maintain their independence and continue to lead active lives.

Even though leflunomide was at least equivalent to methotrexate and sulphasalazine in studies 301US and 301MN ($p<0.01$), the negative results of 302MN confounded any equivalency claim. However, the significant results of the two placebo-controlled trials did allow a claim that leflunomide is more effective than placebo. The claim that leflunomide

slows the structural damage of rheumatoid arthritis was based on paired X-rays taken at baseline and at completion of the study.

Adverse events seen in patients taking leflunomide were generally considered mild to moderate, (according to Hoechst Marion Roussel's consultant, Dr Marc Hochberg of the University of Maryland, who was a member of the US study's drug safety monitoring board). The most frequent adverse event was diarrhoea, in up to 27% of patients in placebo-controlled studies. In 1,339 patients treated in Phase II and III trials, other common adverse events seen were abdominal pain, rash, reversible alopecia, and elevated liver transaminases. Withdrawals for patients randomised to leflunomide were comparable to withdrawals in those who received methotrexate and fewer than those seen with sulphasalazine. The overall incidence of infections was high in the Phase III studies but at the therapeutic doses used in the trials, there was no evidence of more infections in the leflunomide treatment group than in the other study arms.

Liver function test results differed dramatically between studies. In study 301US, more patients on leflunomide had higher alanine transaminase (ALT) and aspartate transaminase (AST) elevations (27.5% and 20.4% respectively) than those on placebo (8.4% and 7.6% respectively) or methotrexate (20.3% and 13.6% respectively). In study 302MN, more patients on methotrexate had higher ALT and AST elevations (48.5% and 35.6% respectively) than patients on leflunomide (21.4% and 15.6% respectively). The contradictory results may have been due to the fact that there were different lengths of treatment, different levels of folate supplementation (over 90% in the US compared with about 10% in Europe) and different monitoring procedures. Elevated liver transaminase levels are the most severe side effect with leflunomide although they are reversible on discontinuation. ACR guidelines for monitoring methotrexate give specific indications for obtaining a liver biopsy, which was performed in the 301US protocol. One patient on leflunomide and one on methotrexate met the recommended biopsy guidelines. Twenty deaths occurred among patients who received leflunomide, compared with 20 on methotrexate, three on sulphasalazine and two on placebo. However, the incidence per 100 patient-years was 0.96 for leflunomide, 2.14 for methotrexate, 1.16 for sulphasalazine and 0.88 for placebo.

Dr David Scott, Professor of Clinical Rheumatology at King's College, London, summarised data from the trials presented at the ACR meeting as follows: He reported that leflunomide produced a significant slowing of progression of rheumatoid arthritis and was shown to interfere at all stages of the disease process, including the early stages. It was clearly effective, and acted rapidly, within the first 6 months of treatment, as documented by X-ray data. Clinical trials in more than 13,000 patients had shown leflunomide to be significantly better than placebo on a range of measures, and equivalent to, or better than, two available DMARDs, methotrexate and sulphasalazine. Dr Scott also noted that leflunomide has a good safety profile, with less need for monitoring than other DMARDs. Side effects most commonly reported in clinical trials include diarrhoea, alopecia, rash and elevated liver enzymes (ALT and AST), so there was a requirement for hepatic function monitoring. In contrast, methotrexate and sulphasalazine both require regular monitoring of hepatic and renal function, as well as regular blood checks. Dr Scott pointed out that such screening raises the cost of overall treatment, adding that for methotrexate the overall cost of treatment and monitoring is estimated at around $2,000 per year. In the US, leflunomide costs around $8 per day, which works out at around $2,848 per year.

Leflunomide is indicated for use in adults in the treatment of active rheumatoid arthritis to reduce signs and symptoms and to reduce structural damage as evidenced by X-ray erosions

and joint space narrowing. It is contraindicated in women who are or who may become pregnant, because of teratogenicity. There is also a warning about hepatotoxicity. Treatment should be initiated with a loading dose of one 100mg tablet per day for 3 days, and then maintained at 20mg/day.

4.3.1.2 Other studies with leflunomide

Leflunomide is also being investigated as an anticancer agent by the US biotech company, Sugen, as SU-101. Early-stage clinical trials are being carried out to determine the efficacy of the product in prostate, brain, ovarian and non-small-cell lung cancers when administered intravenously (*Scrip* 2312, 25 February 1998 p22).

Since many patients cannot take methotrexate or sulphasalazine because of side effects or resistance problems, leflunomide will increase the choice of drugs available to them. It has no life-threatening complications and its side effects are complementary to those of the other drugs, which can affect the lungs and liver.

4.3.1.3 Market potential

Hoechst Marion Roussel estimates that worldwide sales of the drug could reach $444 million. Within around 6 weeks of its US launch, sales were ahead of projections at $9 million.

4.4 Comparison summary of emerging arthritis drugs

The five new drugs are compared in Table 4.4 with respect to cost, route of administration and their advantages and disadvantages.

Table 4.4: Comparison of the major new arthritis drugs reaching the market

Generic name	Type of drug	Route of administration	Annual cost	Advantages	Disadvantages
Etanercept	Anti-TNF (TNF receptor p75 fusion protein)	Subcutaneous injection 25mg twice weekly	$11,440 + pharmacy mark-up	Not considered to be antigenic (although some evidence of anti-etanercept antibodies) An alternative to DMARDs	Unfavourable route of administration Potential problems with infections and malignancies High cost Presently indicated only for patients who have failed on two or more DMARDs
Infliximab	Anti-TNF MAb	Infused at intervals of 8 weeks (3mg/kg)	$5,400–8,000 + $1,500 infusion costs	More effective than etanercept Offers an alternative treatment to DMARDs	Significantly antigenic (must be given with an immunosuppressant eg methotrexate) High rate of infections Undesirable route of administration Not well tolerated Potential problems with malignancies High cost

... continued

Table 4.4: (continued)

Generic name	Type of drug	Route of administration	Annual cost	Advantages	Disadvantages
Celecoxib	COX-2 inhibitor	Oral, 100mg twice daily	$900–1,100	Superior gastrointestinal profile to naproxen and diclofenac No effect on platelet aggregation	Still has potential for renal damage Further data needed on side effects
Rofecoxib	COX-2 inhibitor	Oral once daily (25 or 50mg)	$900–1,100	Superior gastrointestinal profile to established NSAIDs A broader indication than celecoxib due to longer studies on pain relief	Potential for renal damage remains Further data needed on side effects
Leflunomide	DMARD (pyrimidine synthesis inhibitor)	Oral once daily A loading dose of 100mg for 3 days and then 20mg maintenance dose	$3,000	Claimed to delay structural damage Fewer side effects than other DMARDs Does not require monitoring of kidney function and blood cell counts	Requires liver enzyme monitoring Contraindicated in pregnancy Side effects: diarrhoea, alopecia, rash, raised liver enzymes

4.5 Other emerging therapies

4.5.1 Therafectin

Boston Life Sciences has filed data from an additional Phase III trial to support the pending US NDA for its synthetic carbohydrate, Therafectin (amiprilose), for the treatment of rheumatoid arthritis (*Scrip* 2350, 8 July 1998 p25). The original submission, which was filed by what was then Greenwich Pharmaceuticals, was rejected by the FDA in 1994 because it demonstrated convincing evidence of efficacy in only one clinical trial, not the two required for approval. However, the application was not withdrawn. The new data, which were released in early 1999, showed that there was a highly significant difference ($p<0.02$) in the percentage of Therafectin patients meeting the 20% Paulus criteria compared with those on placebo (*Scrip* 2303, 23 January 1998 p23). This is achieved by a 20% improvement in four of the following six criteria: tender and swollen joint scores, duration of morning stiffness, ESR and a two-grade improvement in the patient's and observer's assessment of disease severity.

Discussions on partnerships for the manufacture, marketing and distribution of Therafectin are underway with a number of large companies (*Scrip* 2318, 18 March 1998 p22).

4.5.2 Prosorba column

The first non-drug therapy to treat rheumatoid arthritis is Cypress Bioscience's Prosorba column. It is already approved in the US for the treatment of idiopathic thrombocytopenic purpura (an immune-related bleeding disorder) and has now been approved by the FDA for the treatment of moderate to severe rheumatoid arthritis. It will be used in patients who have failed on or are intolerant of DMARDs.

The column consists of a purified bacterial protein A covalently bonded to silica. The treatment involves a two-and-a-half-hour dialysis procedure once a week, where the patient's blood is filtered through the Prosorba column. Twelve weekly outpatient sessions are recommended, each of which would cost between $700 and $1,000. The patient also needs to purchase a new column for each treatment, priced at $1,090 which brings the total cost per session to $1,790–2,090. This suggests that it is likely to be used only for more severe cases of the condition. In a recently conducted Phase III trial, it was used as third-line therapy for patients with chronic rheumatoid arthritis. The double-blind, placebo-controlled trial enrolled 268 patients and lasted 12 weeks. The primary endpoint was the percentage of patients who achieved a 20% improvement in a composite disease severity score. On an intent-to-treat basis, patients in the Prosorba group performed significantly better than those in the placebo group (33.3% versus 9.3%; p=0.006) and the trial was stopped 1 year earlier than anticipated. The exact mechanism of action of the Prosorba column is unclear. It is known that proteins in the column bind to IgG and immune complexes, removing them from the bloodstream (*Scrip* 2303, 23 January 1998 p21). According to Cypress Bioscience, around 10% of the 2.5 million patients in the US with rheumatoid arthritis do not benefit from the current antirheumatic drugs but, may benefit from the Prosorba column (*Scrip* 2422, 24 March 1999 p18).

4.6 The market potential of the new arthritis therapies

Of all the emerging new therapies for arthritis, US analysts perceive the COX-2 specific agents – celecoxib and rofecoxib – as certain best-sellers. Analysts also believe that Immunex's anti-TNF agent, etanercept, could reach peak sales of $1 billion if certain issues are resolved. However, they are less certain about infliximab and leflunomide.

Analysts views on the potential market for these drugs are given below and their market projections are summarised in Chapter 6.

4.6.1 COX-2 inhibitors

The COX-2 specific inhibitors will compete directly with NSAIDs to offer symptomatic relief in arthritis, for which they are claimed to offer similar efficacy with a much improved gastrointestinal profile (*Scrip* 2393, 4 December 1998 pp20–21). US analysts predict that celecoxib and rofecoxib will revolutionise treatment of osteoarthritis, and also have an impact on rheumatoid arthritis therapy, despite a premium price in the US of $2.50 to $3 per day. There are predictions that the world market for these drugs will grow to $3.3 billion by 2002 ($2.6 billion in the US alone), just 3 years after the first launch.

Southeast Research Partners' analysts, estimate 1999 celecoxib sales to be between $300–$400 million. Analysts at Morgan Stanley predict that they will reach $650–$800 million (*Scrip* 2404, 20 January 1999 p20).

4.6.2 Leflunomide

Leflunomide, the first new DMARD for more than a decade (*Scrip* 2387, 13 November 1998 p19), will compete directly against agents such as methotrexate, sulphasalazine and gold salts. All these older DMARDs have significant side effects, and a large proportion of patients become refractory to treatment. Leflunomide has shown disease modifying activity similar to that of methotrexate, with slightly less toxicity, requiring only liver enzyme monitoring (not kidney and blood cell counts), but with a similar contraindication in pregnancy. Analysts appear to have mixed feelings about leflunomide's potential and some are concerned that physicians will view it simply as a slightly improved version of methotrexate. Morgan Stanley Dean Witter suggested earlier in 1998, that leflunomide's global sales will reach around $500 million by 2003, but analysts at Salomon Smith Barney have lower expectations, forecasting sales of around $236 million by 2002. Anthony Colletta of ABN Amro (UK) is a little more optimistic, forecasting first year sales of $145 million in 1999, rising to $325 million by 2002 and then continuing to grow.

4.6.3 Etanercept

US analysts, Mehta Partners, consider that etanercept has tremendous potential. They feel that it will initially be viewed by US physicians as a powerful last resort drug for severe rheumatoid arthritis but as physicians become more confident that there are no serious side effects, they will gradually use it in less severe cases. Although it is expensive and needs to be administered by subcutaneous injection twice weekly, it represents a totally new approach to the treatment of arthritis. Immunex is expected to file for DMARD status for etanercept next year, which would allow it to be used as a first line treatment. If the product shows usefulness in both methotrexate-naive patients and patients with earlier rheumatoid arthritis, they forecast that it could achieve sales of between $800 million and $1 billion by 2003.

Schroeder & Co's analyst Jami Rubin believes that price is definitely an issue. She predicts that etanercept's sales will reach $100 million in the first year, moving to $250 million in 2000 and peaking at $700 million. She also feels that obtaining DMARD status could mark a turning point, as many physicians considering the use of a DMARD might ignore both methotrexate and leflunomide and move directly to etanercept. However, US analysts from CIBC Oppenheimer are not so positive about etanercept, and say that leflunomide will be a 'formidable competitor' to the Immunex drug. Leflunomide has the advantage of being oral (while etanercept is injectable) and is much cheaper, around $3,000 per year versus $11,000 for etanercept. Also, etanercept is at present indicated for use only in patients who have failed on two or more DMARDs and they are of the opinion that leflunomide could substantially reduce the size of this DMARD-failure population. The analysts point out that etanercept is an expensive injectable product in an environment where competing drugs are given orally, but that Immunex has priced its product with full knowledge that it will be used by some patients who have no other alternatives. They predict 1999 sales for etanercept of $146 million. Despite their strong belief in etanercept's efficacy, the analysts maintain that they still have questions about its long-term safety, since the drug has been associated with infections, anti-nuclear and anti-DNA antibodies, and anti-etanercept antibodies. The analysts are of the opinion that, for etanercept to reach peak sales of $700 million or even $1 billion, it will need to prove its usefulness in treating earlier rheumatoid arthritis, and obtain DMARD

status. It must also overcome potential insurance reimbursement problems. As a home-based, self-injection therapy, it does not meet some third-party reimbursement criteria, although Immunex is working to implement a patient reimbursement programme. On the plus side, however, etanercept is the first anti-TNF agent to reach the market, has demonstrated significant responses in some patients with severe rheumatoid arthritis and appears to be very well tolerated, with only mild injection site reactions.

4.6.4 Infliximab

Although infliximab is also an anti-TNF agent, it differs from etanercept in several respects. Etanercept is a soluble TNF receptor while infliximab is a chimaeric MAb, which accounts for differences in antigenicity and in route of administration. Etanercept has a short half-life, and so is administered twice weekly subcutaneously. Infliximab, on the other hand, can be given at intervals of 8 weeks, but has to be infused, using special non-PVC tubing (see *Scrip* 2387, 13 November 1998 p9). It is also antigenic, with about a quarter of patients developing anti-infliximab antibodies when the drug is used alone. For this reason, it has been given together with methotrexate, which acts as an immunosuppressant and so reduces the antigenic response. Infliximab is already marketed in the US for the treatment of Crohn's disease and is in the late stages of development for the treatment of rheumatoid arthritis. There is speculation that infliximab for rheumatoid arthritis would cost between $5,400 and $8,000 per year, which is cheaper than etanercept. However, the cost of clinic-based infusion, up to $1,500 per year, must be added to this. Some US analysts suggest that the use of infliximab will be limited by safety issues. Mehta Partners maintain that it is less well tolerated than etanercept, with the 3mg/kg dose every 8 weeks (the optimum dose) showing a high rate of infections (33% upper respiratory rate) and headaches (25%). They also believe that longer-term therapy with infliximab will uncover an increasing incidence of immunological disturbances, manifested by human antichimaeric antibodies.

CIBC Oppenheimer analysts also believe that anti-infliximab and lupus-like antibodies may limit chronic use of the drug. They note that in the ATTRACT trial (*Scrip* 2389, 20 November 1998 p24), patients were not tested for antibody formation. Although efficacy did not appear to diminish over time, the trial lasted only 12 months and infliximab was given together with methotrexate. They suggest that the drug's 10-day half-life may also be a problem because inhibition of TNF can interfere with the body's ability to fight infection. However, ABN Amro analysts suggest that infliximab may be more potent than etanercept and that from clinical trial data so far, infliximab seems more effective. Nevertheless, they have adopted conservative sales estimates for infliximab of $35 million in 1999, rising to $110 million in 2001. These projections are lower than those for etanercept which were $20 million for 1998 (after only 2 months on the market), rising to $200 million for 2000. Hambrecht & Quist analysts say that sales of infliximab for the rheumatoid arthritis indication could overtake those for Crohn's disease within 2 years. For Crohn's disease they estimate worldwide sales to start at $28 million in 1998, rising to $125 million by 2000. For rheumatoid arthritis, they predict sales of $21 million for 1999, rising to $157 million by the year 2000.

4.6.5 A final opinion

The US Medical Letter (20 November 1998) commented on the new arthritis therapies. In its opinion, leflunomide improves the signs and symptoms of rheumatoid arthritis and slows progression of the disease, but 'offers no clear advantage over better established and less expensive drugs such as methotrexate'. The publication pointed out that, etanercept and

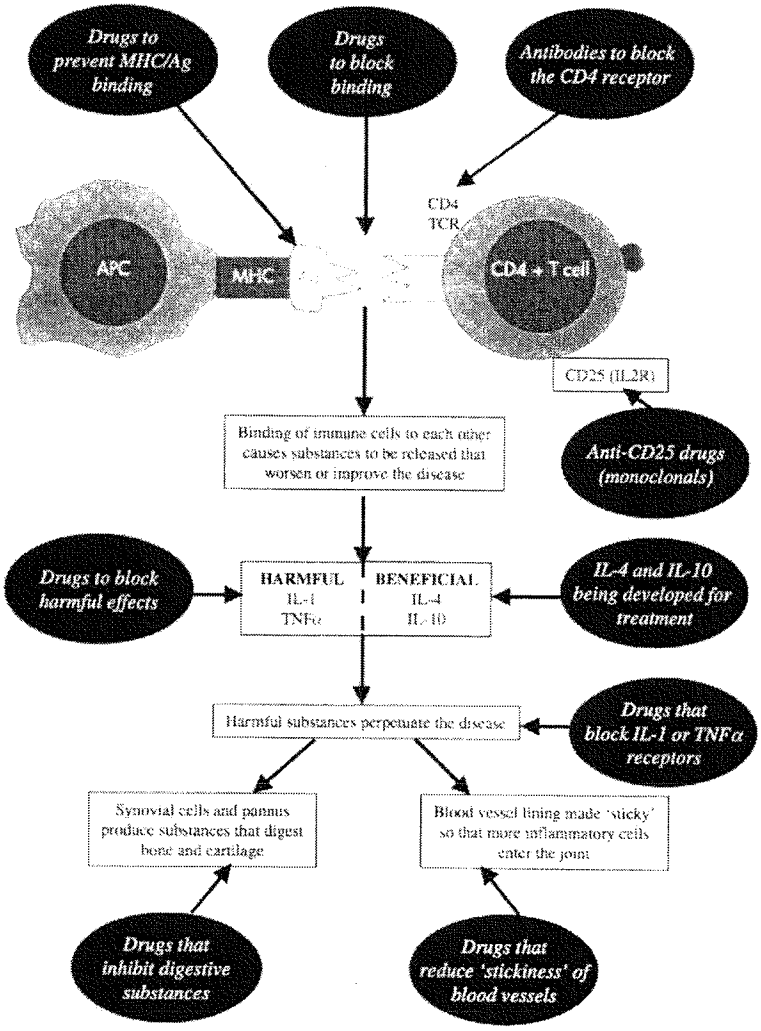
infliximab, appear to be effective in reducing symptoms in active disease refractory to methotrexate or other DMARDs, but whether or not they slow progression of the disease is not known. It has still to be determined whether or not these drugs increase the incidence of other autoimmune diseases, serious infections or malignancies.

CHAPTER 5
FUTURE DRUG THERAPY

Many patients do not respond to or cannot tolerate the established antirheumatic agents. Furthermore, these agents do not cure the disease and achieving a remission is the most that can be hoped for. Consequently, every effort is being made to develop new drugs and find new uses for traditional ones. The recently launched or close-to-launch drugs discussed in Chapter 4 are breaking new ground and are set to make a positive impact on the market (and indeed are already doing so) but a number of companies have other novel therapies in the pipeline some of which may well represent the next wave of ground breaking launches.

Areas being targeted for new rheumatoid arthritis therapeutics are summarised in Figure 5.1.

Figure 5.1: Areas of development for new rheumatoid arthritis therapies



Source: Target Rheumatoid Arthritis, 1997.

Drugs in development are summarised in two tables; Table 5.1 lists the drugs currently in clinical development and Table 5.2 lists those in preclinical development. In the case of the preclinical listings, these are at a very early developmental stage, often for a wide range of potential indications. Only a small proportion of these are likely to be destined for the arthritis market.

MK-663 is a COX-2 inhibitor, under development by Merck for the treatment of osteoarthritis, rheumatoid arthritis and pain. It is the follow-up to rofecoxib and may be more potent and more COX-2 selective. It is expected to enter Phase III clinical trials in mid-1999 for the indications stated (*Scrip* 2434/2435, 5/7 May 1999 p13).

5.1 Selective COX-2 inhibitors

In the wake of successful recent launches, the development of specific COX-2 inhibitors is now a priority for arthritis drug therapy. A second-generation COX-2 inhibitor, valdexcoxib, is under development by Searle (Monsanto) as a follow-up to celecoxib. It will be developed and co-promoted by Pfizer for the treatment of arthritis (*Scrip* 2387, 13 November 1998 p12). Other COX-2 inhibitors in clinical development, listed in Table 5.1, include SC-57666 (Monsanto) and JTE-522 (Japan Tobacco). There are also new formulations of older drugs in the clinical pipeline such as Diclofenac rectal and Diclofenac foam for rectal and topical application respectively.

5.2 Dual acting anti-inflammatory drugs

ML-3000 is an orally-active dual COX and 5-lipoxygenase inhibitor (Dual Acting Anti-Inflammatory Drug or DAAID), originally synthesised by Merckle and under development as an anti-inflammatory agent and analgesic by the EuroAlliance consortium (ASW/Lacer/Merckle). 5-lipoxygenase is the enzyme responsible for the synthesis of leukotrienes. ML-3000 is in Phase II dose-finding trials for rheumatoid arthritis and osteoarthritis.

Phase II trials for rheumatoid arthritis and osteoarthritis are expected this year (1999) on the anti-inflammatory, CI-1004, which also works by dual inhibition of 5-lipoxygenase and COX-2. This dual mechanism of action may provide advantages over COX-2 inhibition alone as a result of enhanced anti-inflammatory efficacy. It could have the gastrointestinal safety of the new COX-2 agents with improved efficacy over current NSAIDs (*Scrip* 2330, 29 April 1998 p8). CI-1004 is under development by Warner-Lambert.

5.3 Nitric oxide NSAIDs

The nitric oxide NSAIDs are drugs which donate nitric oxide to the gastric mucosa to counterbalance the harmful effects of PG deficiency. They may provide an alternative to COX-2 inhibitors since they have shown a good gastrointestinal safety profile in animal studies (*Scrip* 2407, 29 January 1999 p24). The French company, NicOx is developing HCT-1026 which is in Phase II trials.

Table 5.1: Arthritis drugs in clinical development

Product	Originator	Pharmacology	Development stage (for arthritis)	Comment
Diclofenac, rectal, Core	Core Technologies (UK)	COX inhibitor	Clinical trials	Core Technologies is developing a rectal formulation of diclofenac
MX-68	Chugai (Japan)	Dihydrofolate reductase inhibitor Thymidylate synthase inhibitor	Clinical trials	MX-68 is a methotrexate derivative with high specificity for human dihydrofolate reductase. It is in clinical trials in the UK for rheumatoid arthritis
AGT-1	Advanced Biotherapy Concepts (US)	IFN-γ antagonist IFN-α antagonist TNF antagonist	Phase I	AGT-1 is a polyclonal antibody mixture directed against cytokines such as IFN-γ, TNF and IFN-α under development as a treatment for rheumatoid arthritis and other autoimmune diseases
AnergiX	Anergen (US)	T-cell inhibitor	Phase I	AnergiX is a series of protein-based therapeutics, under development for the treatment of autoimmune diseases including rheumatoid arthritis. The agent for rheumatoid arthritis combines a peptide derived from HCgp39 (a human cartilage-derived glycoprotein) with the AnergiX technology
Atiprimod dihydrochloride	AnorMED (Canada)	Immunosuppressant	Phase I	Atiprimod dihydrochloride is the lead compound in a series of azaspirane immunomodulators, under development for the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis, and the prevention of organ transplant rejection
BB-3644	British Biotech (UK)	MMP inhibitor TNF antagonist	Phase I	BB-3644 is the lead compound from a series of dual action TNF/MMP inhibitors (TMIs), under development for treatment of chronic inflammatory diseases, such as MS, rheumatoid arthritis and IBD and cancer
BMS-188667	Bristol-Myers Squibb (US)	CD28 antagonist T-cell inhibitor	Phase I	BMS-188667 is an immunosuppressant, under development for the treatment of psoriasis, transplant rejection, inflammation, allergy and autoimmune diseases such as rheumatoid arthritis (in Phase I) and lupus. It is a soluble antibody which binds with high affinity to B7, a molecule which binds to the CD28 T-cell receptor and co-stimulates T-cell proliferation

CG-1088	Celgene (US)	Phosphodiesterase IV (PDEIV) inhibitor TNF-α antagonist	Phase I	CG-1088 is the lead compound from a series of small, orally-active PDEIV inhibitors (SelCID; Selective Cytokine Inhibitory Drugs), based on key structural features of thalidomide, which have potential in autoimmune diseases such as rheumatoid arthritis. It is under development by Celgene in conjunction with researchers at Rockefeller University, US
CGS-27023A	Novartis (Switzerland)	MMP inhibitor	Phase I	CGS-27023A is an orally administered MMP inhibitor under development for cancer and osteoarthritis
Diclofenac, FOAM-SYS	Poli (Italy)	COX inhibitor	Phase I	Poli is developing an extemporary diclofenac foam formulation using its FOAM-SYS technology for the local treatment of pain and inflammation associated with osteoarthritis and acute traumatic injuries
HSV-tk gene therapy	IntroGene (The Netherlands)	Thymidine kinase stimulant DNA directed DNA polymerase inhibitor	Phase I	IntroGene is developing an adenoviral herpes simplex virus thymidine kinase (HSV-tk) suicide gene therapy for the treatment of rheumatoid arthritis
IL-10	Schering-Plough (US)	IL-10 agonist	Phase I	DNAX (Schering-Plough) has cloned and expressed IL-10. It is a regulator of immune and inflammatory responses and inhibits synthesis of IFN-γ and other cytokines produced by stimulated T-helper cells. Human IL-10 is in Phase I clinical trials for rheumatoid arthritis
Immunoglobulin	Research Corporation Technologies (US)	Immunostimulant	Phase I	Protein Therapeutics is developing human immunoglobulin, which is reactive against autoimmune superantigens, as a therapy for severe rheumatoid arthritis
Ketoprofen transdermal	Noven Pharmaceutfcals (US)	COX inhibitor	Phase I	Noven is developing a ketoprofen transdermal patch for the treatment of soft tissue and sport injuries and local inflammatory incidences of osteo- and rheumatoid arthritis. Phase I trials have been completed
Ketoprofen	Poli (Italy)	COX inhibitor	Phase I	A topical formulation of ketoprofen (ketoprofen plaster) for use in osteoarthritis and musculoskeletal pain. It uses Pacific Pharmaceutical's proprietary plaster formulation system
MRA	Chugai (Japan)	IL-6 antagonist	Phase I	MRA is a recombinant humanised MAb against the human IL-6 receptor. It is indicated for multiple myeloma, rheumatoid arthritis and other IL-6-associated diseases
Paclitaxel	Angiotech (Canada)	Microtubule stimulant	Phase I	Angiotech is developing micellar formulations of paclitaxel for the treatment of rheumatoid arthritis and MS

S-2474	Shionogi (Japan)	PGE2 antagonist Leukotriene B4 antagonist COX-2 inhibitor	Phase I	S-2474 is the lead compound in a series of antioxidant benzylidene derivatives, under development as an anti-inflammatory agent for use in arthritis. It appears to work via a mechanism different from conventional NSAIDs and DMARDs, possibly through the suppression of the COX-2 pathway
SC-57666	Monsanto (US)	COX-2 inhibitor	Phase I	SC-57666 is one of a series of selective COX-2 inhibitors under investigation by Searle (Monsanto) for the treatment of arthritis. It also has anti-inflammatory and analgesic activity. It is hoped that compounds in the series will have improved side effect profiles, providing anti-inflammatory effect without undesirable gastrointestinal tract side effects. It is in Phase I clinical trials in Europe and the US
Soluble TNF receptor 1	Amgen (US)	TNF antagonist	Phase I	Synergen (Amgen) is developing soluble TNF receptor 1 as a second-generation TNF-binding protein for use against rheumatoid arthritis
TBP-I	Yeda (Israel)	TNF antagonist	Phase I	TNF-binding protein I and II (TBP-I and TBP-II) are recombinant human TNF-binding proteins isolated from human urine, under development by Yeda and Ares-Serono as a treatment for rheumatoid arthritis
T-cell receptor peptides	Connetics Corporation (US)	T-cell inhibitor	Phase I	Connetics has acquired exclusive worldwide rights to Xoma's TCR peptide technology and is using the technology to develop TCR peptide-related products to treat chronic connective tissue and autoimmune diseases such as rheumatoid arthritis (Phase I), psoriasis and IBD. The peptides elicit an immune response in regulatory T-cells which release cytokines that selectively suppress the activity of pathogenic T-lymphocytes in certain autoimmune diseases
Thalidomide	Celgene (US)	TNF-α antagonist	Phase I	Thalidomide is launched in the US as Thalomid for use in leprosy patients with erythema nodosum leprosum (painful nodules associated with an immune reaction). Phase I trials in rheumatoid arthritis are underway
TRK-530	Toray (Japan)	Unidentified pharmacological activity	Phase I	TRK-530 is one of a series of methane diphosphonate derivatives under development as an anti-arthritic. A launch is expected in 2007
VX-740	Hoechst Marion Roussel (Germany)	IL-1β converting enzyme inhibitor	Phase I	VX-740 is the lead compound in a series of ICE inhibitors under joint development by Hoechst Marion Roussel and Vertex for the treatment of rheumatoid arthritis
ZD-2315	Zeneca (UK)	MHC class II antagonist	Phase I	ZD-2315 is the lead compound in a series of small molecule inhibitors of MHC class II gene transcription, under development by Zeneca and Boston Life Sciences. It is in Phase I trials for rheumatoid arthritis

Denileukin diftitox	Ligand Pharmaceuticals (US)	IL-2 receptor antagonist	Phase I/II	Seragen (Ligand) has produced denileukin diftitox, the product of a fusion of the adenosine diphosphate (ADP)-ribosyltransferase and membrane translocation domains of the diphtheria toxin gene to a gene whose product targets the IL-2 receptor. It is licensed to Lilly for oncology and has completed Phase I/II trials in rheumatoid arthritis (Seragen)
Gusperimus	Nippon Kayaku (Japan)	B-cell stimulant	Phase I/II	Gusperimus is an analogue of spergualin, launched in Japan for the prevention of renal transplant rejection. It is in Phase I/II trials for rheumatoid arthritis (Bristol-Myers Squibb)
Iloprost	Schering AG (Germany)	Prostacyclin agonist Platelet aggregating antagonist TNF-α antagonist	Phase I/II	Iloprost is a stable epoprostenol analogue, developed by Schering AG for peripheral vascular disease. The slow release oral formulation (iloprost oral) conjugated to β-cyclodextrin clathrate (SH-529) is in Phase I/II trials for rheumatoid arthritis
4162W94	Glaxo Wellcome (UK)	CD4 antagonist	Phase II	4162W94 is a humanised anti-CD4 MAb under development for use in rheumatoid arthritis. It is in Phase II clinical trials
5G1.1	Alexion Pharmaceuticals (US)	C5a inhibitor	Phase II	5G1.1 is a long-acting humanised high-affinity MAb under development for the treatment of lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis and other inflammatory diseases. It prevents the cleavage of human C5 into its proinflammatory complement products
Anakinra	Amgen (US)	IL-1 receptor antagonist	Phase II	Anakinra is a recombinant non-glycosylated IL-1 receptor antagonist expressed in *Escherichia coli*, under development by Synergen (Amgen) for the treatment of rheumatoid arthritis. It is in Phase II trials with methotrexate in rheumatoid arthritis in the US and Europe
Antirheumatic peptides	Peptide Therapeutics (UK)	Unidentified pharmacological activity	Phase II	Peptide Therapeutics is developing antirheumatic peptides for the treatment of rheumatoid arthritis. The tetrapeptide disrupts the complex formed between IgA and alpha1-antitrypsin that leads to the release of tissue-degrading enzymes and cytokines by macrophages and so may alleviate rheumatoid arthritis
Anti-TNF-α Ab	Cambridge Antibody Technology (UK)	TNF-α antagonist	Phase II	Cambridge Antibody Technology and Knoll are developing a recombinant human anti-TNF-α MAb for the treatment of rheumatoid arthritis
CB-2431	KS Biomedix (UK)	Unidentified pharmacological activity	Phase II	KS Biomedix Holdings is developing CB-2431, a combination of two known drugs, for the treatment of osteoarthritis. It is in Phase II trials

CBF-BS2	KS Biomedix (UK)	Glucose-6 phosphate dehydrogenase inhibitor	Phase II	KS Biomedix Holdings is developing CBF-BS2 for the treatment of rheumatoid arthritis. It acts by reversing abnormal increases in glucose-6-phosphate dehydrogenase seen in the synovial lining cells of rheumatoid arthritis sufferers
CDP-571	Celltech (UK)	TNF-α antagonist	Phase II	CDP-571 (Bay-10-3356) is a recombinant humanised antibody against TNF-α, under development for the treatment of TNF-mediated diseases such as rheumatoid arthritis and ulcerative colitis. It is in Phase II trials. The US FDA will give CDP-571 fast-track review status with launch expected in 2000
CGS-25019C	Novartis (Switzerland)	Leukotriene B4 antagonist	Phase II	CGS-25019C is a LTB4 receptor antagonist. It is in Phase II clinical trials for use against rheumatoid arthritis
Clenoximab	IDEC (US)	CD4 antagonist	Phase II	Clenoximab is a PRIMATIZED anti-CD4 antibody under development by IDEC and SmithKline Beecham (as SB-217969) for the treatment of inflammatory diseases. It consists of a CD4-targeting region and an IgG4 constant region. IDEC-151 is the lead antibody selected for the treatment of rheumatoid arthritis
D2E7	Knoll (Germany)	TNF antagonist	Phase II	D2E7 is a humanised MAb directed against human TNF, under development by BASF (parent company of Knoll) for the treatment of rheumatoid arthritis, sepsis and IBD. It is in Phase II clinical trials in rheumatoid arthritis patients
Galantamine	Shire Pharmaceuticals (UK)	Cholinesterase inhibitor	Phase II	The acetylcholinesterase inhibitor, galantamine, is launched for the treatment of Alzheimer's disease and related dementias. It is in Phase II trials for osteoarthritis/rheumatoid arthritis. Galantamine appears to act on the nicotine receptors in the brain, stimulating the release of more acetylcholine
IL-1 receptor	Immunex (US)	IL-1 antagonist	Phase II	Receptech (Immunex) has cloned the receptor for human IL-1 and produced it in a mammalian expression system. It is in Phase I/II trials for asthma and rheumatoid arthritis
IL-1ra gene therapy	MEGABIOS (US)	IL-1 receptor antagonist	Phase II	MEGABIOS is collaborating with researchers from the University of Pittsburgh Medical Center, US, on a gene therapy for rheumatoid arthritis. A viral product has almost completed Phase I/II trials
Immune therapy	Connetics Corporation (US)	Immuno-suppressant	Phase II	Connetics is developing an immune therapy for rheumatoid arthritis

IR-501	Immune Response (US)	T-cell inhibitor	Phase II	A combination of three T-cell receptor peptides plus an adjuvant is under development by Immune Response for rheumatoid arthritis and has been designated IR-501. AI-201, AI-205 and AI-204 are rheumatoid arthritis therapeutic vaccines, also under development, which incorporate T-cell receptor sequences associated with the T-cells involved in the disease. The vaccines stimulate the immune system to attack these destructive T-cells. They may also induce a regulatory condition, protecting the patient from additional tissue destruction
ISIS-2302	ISIS Pharmaceuticals (US)	ICAM-1 antagonist Protein synthesis antagonist	Phase II	ISIS-2302 is an ICAM-1 phosphorothioate antisense oligonucleotide, targeted at the 3'-untranslated region of ICAM-1. It is in Phase II trials in the US and Europe for psoriasis (topical), rheumatoid arthritis, kidney and renal transplant rejection, and ulcerative colitis
JTE-522	Japan Tobacco (Japan)	COX-2 inhibitor	Phase II	JTE-522 is an orally-active, highly selective COX-2 inhibitor, under development by Japan Tobacco for the treatment of rheumatoid arthritis, osteoarthritis and other painful disorders. It is in Phase II trials in Japan
Keliximab	IDEC (US)	CD4 antagonist	Phase II	Keliximab (IDEC-CE9.1) is a PRIMATIZED anti-CD4 antibody which consists of a CD4-targeting variable region and an IgG1 constant region. It is in development for rheumatoid arthritis. A Phase IIIa trial in rheumatoid arthritis was terminated and enrolment suspended due to an unexplained suppression of CD4 cell counts
LeukoVax	Inflammatics (US)	Immunosuppressant	Phase II	LeukoVax is an immunomodulating mono-nuclear cell preparation, under development for the treatment of rheumatoid arthritis. It is in Phase I/II clinical trials in the US
ML-3000	Merckle (Germany)	COX inhibitor 5-lipoxygenase inhibitor	Phase II	ML-3000 is an orally-active dual cyclo-oxygenase and 5-lipoxygenase inhibitor (DAAID), originally synthesized by Merckle and under development as an anti-inflammatory and analgesic by the EuroAlliance consortium (ASW/Lacer/Merckle). It is in Phase II dose-finding trials for rheumatoid arthritis and osteoarthritis
MK-663	Merck (US)	COX-2 inhibitor	Phase II	MK-663 is under development for the treatment of osteoarthritis, rheumatoid arthritis and pain. It is the follow-up to rofecoxib
P54	Phytopharm (UK)	COX inhibitor 5-lipoxygenase inhibitor	Phase II	P54 is an oral formulation of a phytomedicine in development for the treatment of osteoarthritis and gastrointestinal disorders, such as irritable bowel syndrome, Crohn's disease and ulcerative colitis. It has cyclo-oxygenase and 5-lipoxygenase inhibitory activity. It showed disappointing results in a Phase II trial in osteoarthritis patients, with no significant difference between the drug and placebo in the two major endpoints measured (*Scrip* 2431, 23 April 1999 p19)

PASSTNF-α	Verigen (US)	TNF-α antagonist	Phase II	Verigen is developing PASSTNF-α, an anti-TNF porcine antibody preparation, produced using Verigen's PASSIMMUNE gp-48 technology. PASSIMMUNE utilises antibodies directed against MHC class II molecules which prevent foreign antigen presentation and thus rejection of the porcine antibodies. The preparation is being developed for autoimmune diseases, including rheumatoid arthritis
Pentostatin	Warner-Lambert (US)	Adenosine deaminase inhibitor	Phase II	Pentostatin is an adenosine deaminase inhibitor developed for hairy cell leukaemia. It is in Phase II trials for rheumatoid arthritis
SR-31747	Sanofi (France)	IL-1 antagonist TNF antagonist IL-6 antagonist	Phase II	SR-31747 is a ligand of the peripheral sigma receptor on human leucocytes, under development for rheumatoid arthritis. It strongly inhibits the proliferation of activated T-cells and reduces the production of IL-1, IL-6 and TNF. It has no CNS activity. A registration application is scheduled for filing in 2001
Tacrolimus	Fujisawa (Japan)	Calcineurin inhibitor IL-2 antagonist	Phase II	Tacrolimus is a macrolide immunosuppressant isolated from *Streptomyces tsukubaensis*. It forms a complex which shields the active site of calcineurin. It inhibits IL-2 and the expression of IL-2 receptors and is launched for organ transplantation requirements. Tacrolimus is in Phase II trials in Japan and the US for rheumatoid arthritis, myasthenia gravis and lupus nephritis
TAK-603	Takeda (Japan)	Immunosuppressant	Phase II	TAK-603 is an immunomodulatory agent, under development for the treatment of rheumatoid arthritis. It is in Phase II clinical trials in Japan, the US and Europe
TOK-8801	Asahi Chemical (Japan)	Unidentified pharmacological activity	Phase II	TOK-8801 is an antirheumatic immunomodulator, which is in Phase II clinical trials for rheumatoid arthritis
VX-497	Vertex Pharmaceuticals (US)	Inosine monophosphate dehydrogenase (IMPDH) inhibitor	Phase II	VX-497 is an IMPDH inhibitor, under development for the treatment of hepatitis C, asthma, psoriasis, rheumatoid arthritis, systemic lupus erythematosus and organ transplant rejection. IMPDH is required for DNA replication by lymphocytes which, unlike other cells, cannot use alternative enzyme pathways when IMPDH is not available. The 3D atomic structure of IMPDH has been solved and the company has developed novel, orally bioavailable inhibitors of the enzyme
Zileuton	Abbott (US)	5-lipoxygenase inhibitor	Phase II	Zileuton is a 5-lipoxygenase inhibitor, developed as an anti-asthma and anti-inflammatory agent. It is in Phase II trials for rheumatoid arthritis and allergic rhinitis

AI-200	AutoImmune (US)	Collagen agonist	Phase III	AI-200 is solubilised monomeric type II chicken collagen, under development for the treatment of rheumatoid arthritis. It is in US Phase III trials in 800 rheumatoid arthritis patients. Phase II safety and efficacy trials in 1,200 patients with severe rheumatoid arthritis have been completed
Bay-12-9566	Bayer (Germany)	Stromelysin inhibitor MMP-2 inhibitor MMP-3 inhibitor	Phase III	Bay-12-9566 is a stromelysin inhibitor, under development for the treatment of osteoarthritis and the inhibition of cancer metastasis
CKD-461	Chong Kun Dang (South Korea)	Immunosuppressant	Phase III	CKD-461 is an immunosuppressant, developed for use in organ transplantation. It is launched in South Korea as Cipol-N. It is in Phase III clinical trials for rheumatoid arthritis, nephrotic syndrome and aplastic anaemia
Eltenac	Byk Gulden (Germany)	COX inhibitor	Phase III	Eltenac is a potent NSAID with analgesic and antipyretic activity. It is licensed to Luitpold (Sankyo) which is developing a topical gel formulation (Phase III trials) for transdermal use in osteoarthritis
Mycophenolate mofetil	Roche (Switzerland)	Immunosuppressant	Phase III	Mycophenolate mofetil (CellCept) is an immunosuppressant which was isolated from a fungus and chemically modified to improve oral absorption. It is launched for use with other immunosuppressants in the prevention of acute rejection. It is in Phase III clinical trials for rheumatoid arthritis
Pelubiprofen	Sankyo (Japan)	T-cell stimulant	Phase III	Pelubiprofen (CS-670) is an oral anti-inflammatory and analgesic. Expected therapeutic indications include rheumatoid arthritis and osteoarthritis
Reumacon	Conpharm (Sweden)	Microtubule inhibitor β-amyloid precursor protein antagonist	Phase III	Reumacon is a podophyllotoxin-containing compound, under development for the treatment of advanced chronic rheumatoid arthritis
Rimexolone	Akzo Nobel (Germany)	Lipocortin synthesis agonist Arachidonic acid antagonist Immunosuppressant	Phase III	Rimexolone is a topical corticosteroid which has a long duration of anti-inflammatory effect, high corticoid receptor affinity and a superior systemic safety profile. It is launched in the US by Alcon which has worldwide rights for use in ophthalmology and otology. Phase III clinical trials for intra-articular use in rheumatoid arthritis and osteoarthritis have been completed

Sonatimod	Taisho (Japan)	IL-1 antagonist IL-6 antagonist Interstitial collagenase inhibitor	Phase III	Sonatimod (KE-298) is the lead compound of a series of 2-penicillamine derivatives, under development by Taisho as an immunomodulator with potential in rheumatoid arthritis for which it is in Phase III trials
T 614	Toyama (Japan)	IL-1β antagonist IL-6 antagonist IL-8 antagonist	Phase III	T-614 is an oral anti-inflammatory agent. It suppresses the production of IL-1, IL-6, IL-8 and TNF. It is licensed to Eisai for co-development and co-marketing in Japan and is in Phase III clinical trials in Japan as an antirheumatic agent

Table 5.2: Arthritis drugs in preclinical development

Product	Originator	Pharmacology	Comment
T-cell inhibitors	Active Biotech (Sweden)	T-cell inhibitor	Lund Research Centre (Active Biotech) is investigating T-cell inhibitors for use in transplant rejection and rheumatoid arthritis
Phosphosugars	Anutech (Australia)	Lymphocyte inhibitor	Anutech and the John Curtin School of Medical Research, Australia, are developing phosphosugars, including mannose-6-phosphate, as potent anti-inflammatory agents. Phosphosugars inhibit the passage of leukocytes through the vascular membrane to the site of inflammation and are expected to be free of the side effects associated with conventional anti-inflammatory drugs. Anutech is developing oral phosphosugar formulations and MAbs, and investigating phosphosugar receptor analogues. In preclinical studies, they have been effective in the treatment and prevention of passively-transferred arthritis and experimental autoimmune encephalomyelitis. They have potential in rheumatoid arthritis, MS and asthma
Cathepsin B inhibitors	AxyS (US)	Cathepsin B inhibitor	AxyS is developing cathepsin B inhibitors for the treatment of rheumatoid arthritis and cancer
Cysteine protease inhibitors	British Biotech (UK)	Cysteine proteinase inhibitor	British Biotech and SynPhar (Taiho) are collaborating on the discovery and synthesis of cysteine protease inhibitors with potential in the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis and cancer
Aggrecanase inhibitors	Celltech (UK)	MMP inhibitor	Celltech, in collaboration with Zeneca, is developing aggrecanase inhibitors for the treatment of osteoarthritis. The inhibitors were identified from a MMP inhibition programme. Aggrecan is the predominant proteoglycan component of cartilage
Retroviral vector	Chiron (US)	Not applicable	Chiron-Viagene (Chiron) is developing high-titre murine leukaemia virus-based retroviral vectors for the delivery of exogenous genes to inflamed joints affected by rheumatoid arthritis
CMTs	CollaGenex (US)	MMP inhibitor	CollaGenex is developing chemically modified tetracycline compounds using the proprietary tetracycline technology licensed from the Research Foundation of the New York State University, Stony Brook, US. The compounds may have potential in the treatment of rheumatoid arthritis, osteoporosis and diabetic nephropathy
Drugs targeting rheumatoid and osteoarthritis	CombiChem (US)	Unidentified pharmacological activity	Sumitomo, in collaboration with CombiChem, is investigating compounds which act on a molecular target which has a fundamental role in rheumatoid and osteoarthritis

Isoxazoline derivatives	DuPont (US)	Vitronectin antagonist; integrin antagonist; angiogenesis inhibitor	This is one of a series of isoxazoline derivatives under investigation by DuPont as vitronectin receptor antagonists with potential in restenosis, tumour metastasis, osteoporosis and rheumatoid arthritis
Sultam inhibitors of MMPs	DuPont (US)	MMP inhibitors	This is a compound in a series of sultam inhibitors of MMP, under investigation by DuPont. It may have potential in the treatment of arthritis, cancer, ocular disease and periodontal disease
TNF-α convertase inhibitors	DuPont (US)	TNF convertase inhibitor	This is a compound in a series of succinate-based TNF-α convertase inhibitors, under investigation by DuPont. It may have potential in inflammatory diseases such as rheumatoid arthritis
MDX-CD4	Eisai (Japan)	Unidentified pharmacological activity	MDX-CD4 is a human MAb, under joint development by Eisai and Medarex for the treatment of rheumatoid arthritis and other autoimmune diseases. It was developed using Medarex' transgenic mouse strain, HuMAb-Mouse
IL-8 modulators	Fournier (France)	CXC chemokine receptor 1 antagonist; CXC chemokine receptor 2 antagonist	Fournier is developing a series of IL-8 modulators for the treatment of psoriasis, arthritis, adult respiratory distress syndrome and irritable bowel syndrome. The compounds act as CXCR1 and CXCR2 antagonists
GEMM-1 antagonists	GEMMA Biotechnology (Canada)	GEMM-1 antagonist	GEMMA Biotechnology is investigating antagonists of GEMM-1, a proinflammatory peptide which is associated with cartilage-destroying cells, for potential use in arthritis
Inhibitors of cytokine activation	Genetics Institute (US)	Phospholipase A_2 inhibitor	Genetics Institute has cloned several enzymes, including cytoplasmic PLA_2, which are involved in cellular activation. Drugs which inhibit these enzymes may have potential in the treatment of rheumatoid arthritis and other diseases. They are in preclinical development
GW-353430	Glaxo Wellcome (UK)	CD23 antagonist	GW-353430 is an anti-CD23 MAb, under preclinical development by Glaxo Wellcome for rheumatoid arthritis
Inhibitors of leukocyte adhesion and migration	Hoechst Marion Roussel (Germany)	Very late-acting (VLA) antagonist	Hoechst Marion Roussel is investigating a series of compounds that bind to VLA-4 adhesion receptors. They inhibit the adhesion and migration of leukocytes and have potential in the treatment of rheumatoid arthritis and allergic disorders
Antisense compounds	Hybridon (US)	Protein synthesis antagonist; apoptosis agonist	Hybridon and Searle (Monsanto) are co-developing a series of antisense compounds, as immunomodulators for use in rheumatoid arthritis, transplant rejection, cancer and cardiovascular disease

Caspase I protease inhibitors	Idun (US)	IL-1β-converting enzyme inhibitor	Idun is developing orally-bioavailable caspase I protease inhibitors for use in arthritis and septic shock. Caspase I (also known as IL-1β-converting enzyme (ICE)) is the protease responsible for cleavage of pro-IL-1β and pro-IL-18, which are involved in inflammation, including rheumatoid arthritis, IBD and septic shock
IPL-423	InflaZyme (Canada)	Transcription factor AP-1 inhibitor	IPL-423 (Bispan) is an activator of specific kinase regulator of AP-1 transcription factor, under development by InflaZyme for the prevention and treatment of rheumatoid arthritis. It is an analogue derived from a new class of compounds, IZP-96001, and is designed for once-daily, parenteral or topical administration
Cytokine inhibitors	Japan Tobacco (Japan)	IL-1β antagonist; TNF antagonist; IL-8 antagonist	The most promising compound in a series of amide derivatives is under investigation by Japan Tobacco as a cytokine inhibitor useful for the treatment of arthritis caused by rheumatic diseases or gout
RWJ-68354	Johnson & Johnson (J&J)(US)	P38 kinase inhibitor	RWJ-68354 is a p38 kinase inhibitor, under development by RW Johnson (J& J) for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis, IBD and psoriasis
KB-R7785	Kanebo (Japan)	MMP inhibitor; TNF-α antagonist	KB-R7785 is an orally-available inhibitor of MMPs, TNF-α and Fas ligand (FasL), under development by Kanebo as an anti-arthritic. It is not in active development for immune disorders
EI-1507-1	Kyowa Hakko (Japan)	IL-1β converting enzyme inhibitor	EI-1507-1 and its analogue EI-1507-2 are ICE inhibitors, isolated from the culture broth of *Streptomyces sp*, under investigation by Kyowa Hakko for the potential treatment of rheumatoid arthritis, inflammation and septic shock
KF-20444	Kyowa Hakko (Japan)	Unidentified pharmacological activity	KF-20444 is under development by Kyowa Hakko as a treatment for rheumatoid arthritis and other autoimmune diseases
CCR1 inhibitors	LeukoSite (US)	CC chemokine receptor 1 antagonist; CXC chemokine receptor 3 antagonist; CXC chemokine receptor 1 antagonist	LeukoSite, Kyowa Hakko and Warner-Lambert are developing small molecule inhibitors of the chemokine receptors CCR1, CXCR3 and CXCR1 for the treatment of chronic inflammation, atherosclerosis, rheumatoid arthritis, myocardial infarction, MS and psoriasis
Monocyte chemoattractant protein-1 (MCP-1) inhibitor	LeukoSite (US)	MCP-1 antagonist; 5 lipoxygenase inhibitor	LeukoSite is developing inhibitors of MCP-1 for the treatment of atherosclerosis and rheumatoid arthritis

Fc receptor antagonists	Medical Innovations (US)	Immunoglobulin Fc receptor antagonist	Medical Innovations, in collaboration with the Austin Research Institute, Melbourne, Australia, is developing immunoglobulin Fc receptor antagonists for the treatment of allergic and inflammatory conditions, including rheumatoid arthritis, systemic lupus erythematosus, immune thrombocytopenia and Dengue fever. Fc receptors are present on the surface of inflammatory cells and mediate their activation in autoimmune states when bound by autoantibody immune complexes. Fc receptor antagonists in development include soluble recombinant receptors (for all indications), anti-Fc MAbs (for rheumatoid arthritis, allergy and thrombocytopenia) and small molecule drugs (for rheumatoid arthritis and allergy)
NOX-200	Medinox (US)	Inducible nitric oxide synthase stimulator; inducible nitric oxide synthase inhibitor	NOX-200 is a low molecular weight, orally-active nitric oxide scavenger, under development by Medinox as a chronic treatment for rheumatoid arthritis, juvenile-onset diabetes and other inflammatory diseases
Cytogenin	Mercian (Japan)	IL-1α agonist; IFN-g agonist; GMCSF agonist	Cytogenin is an antibiotic isolated from *Streptoverticillium eurocidicum*, under development by Mercian as a potential anti-arthritic and anticancer agent. It enhances the production of IL-1α by macrophages and IFN-γ and GM-CSF by spleen cells. It does not enhance the production of TNF-α by macrophages and IL-6 by macrophages and spleen cells
Arthritis therapy	Merck (US)	MHC class II antagonist	ImmuLogic has transferred its HLA blocking technology to Merck for the development of compounds which prevent or treat rheumatoid arthritis. Products resulting from the technology will be developed by Merck. ImmuLogic was following two approaches: HLA blocking and peptide immunotherapeutics
GR-373	Merck (US)	Cysteine protease inhibitor; bone formation stimulant	GR-373, GR-375 and GR-377 are selected compounds in a series of anthraquinone-derived human cysteine protease inhibitors, under development by Abiogen (Merck) for the treatment of osteoarthritis
L-758354	Merck (US)	Stromelysin inhibitor	Merck is investigating a series of N-(mercaptoacyl)peptidyl derivatives as potential matrix metalloendoproteinase inhibitors. This type of compound inhibits the degradation of major components of articular cartilage and basement membrane, preventing degenerative diseases such as arthritis, periodontal disease, corneal ulceration and certain cancers
Naproxen	Mimetix (US)	COX inhibitor	Mimetix is developing intramuscular formulations of the NSAID, naproxen (Nanox)
Valdecoxib	Monsanto (US)	COX-2 inhibitor	Valdecoxib is a second-generation COX-2 inhibitor, under development by Searle (Monsanto) as a follow-up to celecoxib for the treatment of arthritis

TNF release inhibitors	Novartis (Switzerland)	TNF antagonist	Novartis is investigating a series of 3-imino-4-oxo-1,7-diolic acid (7-N-hydroxy)diamide derivative TNF release inhibitors for the treatment of autoimmune and inflammatory diseases, such as MS and rheumatoid arthritis
TSG-6	NYU Medical Center (US)	Unidentified pharmacological activity	Researchers at the New York University Medical Center have identified TSG-6, a 35kDa protein, which is a mediator of the inflammatory process. Its secretion is induced by TNF, IL-1 and lipopolysaccharide. High levels of TSG-6 have been found in the synovial fluid of arthritis patients
CP-99994	Pfizer (US)	Substance P antagonist; neurokinin 1 antagonist	CP-99994 is a substance P antagonist under development by Pfizer for the treatment of arthritis, asthma and IBD
MMP inhibitors	Pharmacia & Upjohn (UK)	MMP inhibitor	This is the most promising compound in a series of thiadiazole derivatives acting as MMP inhibitors, under investigation by Pharmacia & Upjohn. It has potential in osteoarthritis, rheumatoid arthritis, periodontitis, gingivitis, tumour metastasis and ulcers
IL-8 inhibitors	Pharmacopeia (US)	IL-8 antagonist	Pharmacopeia is investigating a series of small molecule inhibitors of IL-8, as potential therapeutics for a wide range of diseases. Potential indications include rheumatoid arthritis, asthma, idiopathic pulmonary fibrosis, cardiac reperfusion, Crohn's disease and cancer
Small molecules using Phytera's ExPAND technology	Phytera (US)	Unidentified pharmacological activity	Phytera and Tsumura are jointly-developing small molecules for the treatment of rheumatoid arthritis and allergies. Phytera's plant cell culture extract library is being screened by Tsumura
POL-641	Polifarma (Italy)	MMP inhibitor; TNF-α antagonist	POL-641 is the lead compound of a series of low molecular weight orally-active peptidomimetics with strong inhibitory effects on MMPs, under development by Polifarma. POL-641 has potential use in various inflammatory diseases in which TNF-α release is implicated. It has been tested in animal models of inflammatory disorders and tumour spread. Related orally-active compounds are being studied in preliminary tests for tumour invasion and immune disorders
CD4	Procept (US)	CD4 antagonist	Procept is developing CD4-binding inhibitors as immunosuppressants. Preclinical studies are underway to identify CD4-binding inhibitors. No investigational new drug (IND) application has been filed for a drug candidate from this group for the treatment of rheumatoid arthritis although compounds are undergoing further investigation
DHODH inhibitors	Procept (US)	Hydroorotate dehydrogenase inhibitor	Procept is developing immunosuppressives targeting the intracellular T-cell enzyme dihydroorotate dehydrogenase (DHODH), which is involved in activating the immune response, for the treatment of immune disorders such as rheumatoid arthritis, and to prevent transplant rejection

PGE-2946979	Procter & Gamble (US)	MMP inhibitor	PGE-2946979 is the lead compound in a series of piperazine-based MMP inhibitors, under investigation by Procter & Gamble for the treatment of osteoarthritis
PS-508	ProScript (US)	MMP-3 inhibitor	PS-508 is a selective non-hydroxamic acid inhibitor of MMP-3, under investigation by ProScript. It may have potential for the treatment of arthritis, IBD and periodontal disease. It is a peptidyl derivative of 5-amino-1,3,4-thiadiazole thione
PS-519	ProScript (US)	Proteasome inhibitor	PS-519 is the lead compound in a series of a class of lactone/lactacystin analogue-based proteasome inhibitors, under development by ProScript as anti-inflammatory agents. The compounds have potential in chronic inflammatory diseases such as rheumatoid arthritis, asthma and IBD
Monoclonal antibody	Protein Design Labs (US)	Monoclonal antibody	Protein Design Labs is developing a humanised mouse MAb, targeting a MHC class II protein, for the treatment of rheumatoid arthritis and other autoimmune diseases
RPR-132294	Rhône-Poulenc Rorer (France)	PDEIV inhibitor; TNF antagonist	RPR-132294 and RPR-132703 are members of a series of PDEIV inhibitors, structurally related to piclamilast, under development by Rhône-Poulenc Rorer for the treatment of arthritis and as an oral asthma therapy. The series is selective for the low-affinity (over the high-affinity) rolipram-binding site
RS-130830	Roche (Switzerland)	Neutrophil collagenase inhibitor; stromelysin inhibitor; gelatinase inhibitor	RS-130830 is a second-generation selective collagenase-3 inhibitor, under development by Roche for osteoarthritis
5-lipoxygenase inhibitors	Servier (France)	5-lipoxygenase inhibitor	This is the most promising compound in a series of 5-lipoxygenase inhibitors, under investigation by ADIR (Servier) as anti-inflammatory agents. They may have potential in the treatment of arthritis, colitis and psoriasis
Inhibitors of COXs and lipoxygenases	Servier (France)	5-lipoxygenase inhibitor; COX inhibitor	This is a representative compound from a series of bis-phenyl thiophenes with COX and lipoxygenase inhibitory activities, under development by ADIR (Servier) as an anti-inflammatory agent. The compounds are distinct from those in Servier's other anti-arthritis programmes
SANT-7	Sigma-Tau (Italy)	IL-6 antagonist	An IL-6 receptor antagonist under development for the treatment of multiple myeloma, B lymphomas, rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus and psoriasis

AP-1 inhibitors	Signal Pharmaceuticals (US)	Transcription factor AP-1 inhibitor	Signal, in collaboration with Tanabe, is investigating transcription factors and their activation pathways as targets for small-molecule therapies. Signal has isolated the enzymatic regulator of AP-1, the transcription factor which regulates T-cell response in rheumatoid arthritis and osteoarthritis. AP-1 activates the synthesis of a number of cytokines, including IL-1, IL-2, TNF and IL-8, and Signal is screening for inhibitors of AP-1 transcription for use in rheumatoid arthritis, osteoarthritis and IBD. AP-1 induces IL-2, a critical element, along with neutrophil activation in the pathology of rheumatoid arthritis. It also regulates production of proteolytic enzymes, such as collagenases and stromelysin in neutrophils and chondrocytes, which cause joint degeneration in osteoarthritis
SP-100030	Signal Pharmaceuticals (US)	Transcription factor NF-kappa B (NFκB) inhibitor; transcription factor AP-1 inhibitor; apoptosis agonist	SP-100030 is the lead compound of a series of dual-inhibitors of the transcription factors NFκB and AP-1, under development by Signal in collaboration with Tanabe Seiyaku for the treatment of inflammatory and autoimmune diseases, and for use in transplantation. NFκB regulates production of the proinflammatory cytokines, IL-1, TNF and IL-8, as well as cell adhesion molecules including ICAM, endothelial-leukocyte adhesion molecule (ELAM) and vascular cell adhesion molecule (VCAM), all of which mediate the inflammatory response in a variety of diseases. The companies are developing small molecules which block NFκB for the treatment of rheumatoid and osteoarthritis, IBD, cancer, neurological disorders and viral diseases
Methotrexate analogues	SRI International (US)	Dihydrofolate reductase inhibitor	SRI International and the Sloan-Kettering Institute for Cancer Research, New York, US, are developing methotrexate analogues for the treatment of rheumatoid arthritis. The analogues are being evaluated by an undisclosed company. Over 60 analogues have been tested, from which several compounds have been chosen for further investigation which have advantages over methotrexate
3-benzothiepin-2-carboxamide derivatives	Takeda (Japan)	Bone formation stimulant	This is one of a series of 3-benzothiepin-2-carboxamide derivatives, under investigation by Takeda for the treatment of osteoporosis and osteoarthritis
TMC-2A	Tanabe Seiyaku (Japan)	Dipeptidyl peptidase IV inhibitor	TMC-2A, TMC-2B and TMC-2C, isolated from *Aspergillus oryzae* A374, are dipeptidyl peptidase IV inhibitors, under development by Tanabe Seiyaku for the treatment of immunological diseases involving T-cell activation, such as rheumatoid arthritis
TBC-3342	Texas Biotechnology (US)	VLA antagonist	TBC-3342 is a non-peptidic small molecule inhibitor of VLA-4, under development by Texas Biotechnology for the treatment of rheumatoid arthritis
TBC-772	Texas Biotechnology (US)	VLA antagonist	TBC-772 is the lead compound from a series of modified cyclic peptides, under investigation by Texas Biotechnology. It is being used to develop better clinical candidates as VLA-4 (integrin alpha4beta1) inhibitors. It may have potential in the treatment of atherosclerosis, asthma, rheumatoid arthritis and MS

Peptide-based cell-targeting system	TheraTech (US)	Unidentified pharmacological activity	TheraTech is developing a peptide-based cell-targeting system for the delivery of cytotoxic and/or immunosuppressant drugs directly to immune cells activated in rheumatoid arthritis
YT-146	Toa Eiyo Ltd (Japan)	Tyrosine kinase inhibitor	YT-146 is an adenosine A_2 agonist, under joint-development by Toa Eiyo and Yamasa Corporation. It is in development as an anti-inflammatory and as an immunological agent
VX-745	Vertex (US)	P38 kinase inhibitor	Vertex and Kissei Pharmaceutical have selected a lead p38 mitogen-activated protein (MAP) kinase candidate, VX-745, to enter preclinical studies for the treatment of inflammatory diseases. The oral product, which has been shown to block disease progression in animal models of rheumatoid arthritis and stroke, is expected to enter trials in 1999
CI-1004	Warner-Lambert (US)	5-lipoxygenase inhibitor; COX inhibitor	CI-1004 is a dual inhibitor of 5-lipoxygenase and COX-2, under development by Warner-Lambert for rheumatoid arthritis and osteoarthritis
ICE inhibitors	Warner-Lambert (US)	IL-1β converting enzyme inhibitor	Warner-Lambert and Knoll are jointly developing inhibitors of ICE as potential treatments for inflammatory and neurodegenerative diseases such as Alzheimer's and rheumatoid arthritis, and for other conditions such as septic shock. The programme is at the research stage. ICE generates the active form of IL-1β which is a key mediator in these conditions
PD-98059	Warner-Lambert (US)	MAP kinase inhibitor	PD-98059 is the lead compound in a series of inhibitors of the ERK cascade, under development by Parke-Davis (Warner-Lambert). It binds the inactive form of MAP kinase-1 and has potential in treating dysregulated cellular proliferation in rheumatoid arthritis or other chronic inflammatory diseases
Inhibitors of cytokine activation	Xenova (UK)	Unidentified pharmacological activity	Xenova and Suntory are jointly investigating small molecule drugs for the treatment of rheumatoid arthritis using Xenova's microbial screening technology, ASSET, to identify active compounds with ability to prevent cytokine activation of cells from its collection of microbial and plant extracts
ZD-7349	Zeneca (UK)	VLA antagonist	ZD-7349 is a VLA-4 antagonist, under development by Zeneca for the treatment of arthritis and MS

5.4 New DMARDs

Angiotech is developing a micellar formulation of the anticancer drug, paclitaxel, to be used with or as a substitute for methotrexate. It has begun Phase I testing for rheumatoid arthritis and MS. In preclinical animal studies it has been shown to be effective as a treatment for inflammatory arthritis by reducing clinical signs of the disease including inflammation, swelling, angiogenesis, bone erosion and cartilage destruction. With dose reduction and reformulation, the company hopes to reduce or eliminate many of the toxicities associated with the drug. One significant effect of the drug is its inhibition of angiogenesis and it is a potent inhibitor of the formation of the new blood vessels that support joint inflammation. A Phase I trial enrolling 15 patients is underway (Angiotech press release, 11 June 1998).

Paclitaxel (the world's top-selling anticancer drug with sales of $941 million in 1997) has potential activity against several chronic inflammatory diseases (*Scrip* 2350, 8 July 1998 p27).

CellCept (mycophenolate mofetil) is an immunomodulator from Roche, approved by the FDA for organ transplant reciepients. It has been studied in clinical trials, the results of which were presented at the ACR meeting at San Diego, US, in November 1998. Schiff and Leishman (1998a) reported the results of a randomised double-blind, placebo-controlled study in 153 patients who had completed 9 months of treatment with CellCept (1g or 2g twice daily) in a preceding controlled dose-comparative trial. The researchers compared the time to rheumatoid arthritis flare. This was determined by an increase in tender and swollen joint counts of >9 and >5 respectively and a worsening of investigator and patient global scores by one grade. Patients then either continued their previous CellCept dose or switched to placebo (low placebo matching the 1g dose of CellCept and high placebo matching the 2g dose). After the first 4 weeks of the study, the proportion of patients withdrawing for flare was lower in both CellCept-treated patient groups compared with the placebo groups. The values were 18% and 15% in the 1g and 2g CellCept-treated groups compared with 39% and 47% in the low and high placebo groups. There were no deaths or serious adverse events.

Schiff and Leishman (1998b) also reported two long-term open label studies of 2 and 3 years duration designed to examine the long-term safety of the drug. The trials enrolled 325 patients (244 women and 81 men). CellCept was administered at doses between 0.5g twice daily and 2g twice daily.

Adverse events which led to withdrawal from treatment occurred in 16% of patients. These were primarily gastrointestinal disturbances, respiratory events, haematological abnormalities and neoplasias. The main treatment-limiting adverse effects were non-serious gastrointestinal events such as diarrhoea. The researchers concluded that CellCept in a dose range of 0.5–2.0g twice daily was well tolerated in the long-term treatment of rheumatoid arthritis.

5.5 MAbs

MAbs bind to their targets with high specificity, making them eminently suitable as therapeutic agents. In the inflammatory environment of rheumatoid arthritis, there are a number of therapeutic targets which can be exploited by this approach. These include the MHC molecule, CD4+ lymphocytes, IL-1 and TNF-α. According to Choy *et al* (1998), inhibiting targets at the apex of the pathogenic pyramid is likely to be more disease specific and their suppression more likely to lead to sustained clinical improvement. However, not enough is known about these mechanisms which makes targeting them difficult. In contrast,

targeting mediators at the base of the inflammatory cascade, which are more directly responsible for the symptoms and signs of inflammation, is more inclined to produce effective anti-inflammatory therapies and lead to rapid disease improvement. Nevertheless, these therapies will not be disease specific, are likely to be transient in their effects and may lead to general immunosuppression.

A list of MAbs which have been used in rheumatoid arthritis is presented in Table 5.3. They can be divided into those that inhibit cytokines, those that bind to adhesion molecules and those that target MHC molecules and T-cells.

Table 5.3: MAbs used in rheumatoid arthritis

Main target	Name	Type of MAb
Cytokines		
TNF-α	CA2 (infliximab)*	Chimaeric
	CDP-571/Bay103356	Humanised
IL-6		Murine
Adhesion molecules		
ICAM-1	BIRR-1	Murine
T-cells		
CD7		Murine and chimaeric
CD5	CD5-PLUS	Murine immunotoxin
IL-2R		Murine
CDw52	Campath-1H	Humanised
CD4 depleting	B-F5	Murine
	16H5	Murine
	VIT-4	Murine
	MT151	Murine
	cM-T412	Chimaeric
Non-depleting anti-CD4	IDEC-CE9.1/SB-210396	Humanised
	4162W94	Humanised

Source: Choy et al. *1998.*
*Note: *See Chapter 4.*

Initially MAbs were mainly murine in origin and when administered to patients, the recipients developed human-anti-mouse antibody responses (Kavanaugh *et al*, 1994). This meant that repeated treatment became less effective and there was a risk of anaphylaxis. However, synthetic chimaeric and humanised preparations are now available. In the chimaeric preparations only the murine Fc is replaced by a human sequence where as in the humanised preparations both the Fc region and the framework region of the antigen-binding site is replaced by human sequences. These MAbs are less immunogenic and more suitable as therapeutic agents. More recently, phage libraries have been used to generate completely human MAbs (Marks & Marks, 1996).

The anti-TNF-α MAb, infliximab, in development by Centocor has been discussed in Section 4.2.1. Centocor is also developing two MAbs against IL-6 and IL-8 for the treatment of autoimmune and inflammatory diseases, such as ulcerative colitis, asthma, psoriasis, bone re-absorption due to osteoporosis, and rheumatoid arthritis. Clinical trials are due to begin in 2000 (*Scrip* 2387, 13 November 1998 p9).

Recently, T lymphocytes and their associated cell surface molecules have been the targets of many biological agents designed specifically to interfere with cell function. These include

MAbs directed against particular cell surface markers expressed on T-cells, for example, CD4, CD7, CD5, CD52 and agents directed at the IL-2 receptor (Moreland *et al*, 1997b).

5.6 Cytokines

Anticytokine therapy for rheumatoid arthritis has now reached the clinic, heralded by the development of the anti-TNF biological agents that are proving to be effective in treating the disease (see Section 4.2). TNF-α is of particular interest because of its ability to induce the proliferation of synoviocytes and to enhance their production of PGs, MMPs and other cytokines. Therapy directed at TNF-α includes the use of antibodies or soluble receptors that bind TNF-α and block its activity. However, TNF-α is only the first target to be evaluated. Blockade of IL-1 with soluble IL-1 receptors or the soluble IL-1 receptor antagonist protein (Bresnihan *et al*, 1998) is under investigation as is the blockade of the IL-6 receptor. Other cytokines, such as IL-10 and IL-4 have natural anti-inflammatory activity and are also in clinical development. Although these agents are currently being evaluated individually, optimal treatment may require a combination of treatments which mimic the complex nature of the cytokine pathway.

Cytokine targets under investigation and potential therapeutic agents are listed in Table 5.4.

Table 5.4: Anti-cytokine therapy under investigation for rheumatoid arthritis

Target cytokine	Therapeutic agent
TNF-α	Anti-TNF-α antibody
	Soluble p55 receptor
	Soluble p75 receptor
	TNF-converting-enzyme inhibitor
IL-1	Soluble type I receptor
	Soluble type II receptor
	ICE inhibitors
	IL-1 receptor antagonist
IL-6	Anti-IL-6 receptor antibody
Anti-inflammatory cytokines	IL-10, IL-4
IL-1 and TNF-α	Signal transduction inhibitors (p38 MAP kinase)
	Transcription factor inhibitors

5.6.1 Interleukin-6 antagonists

Members of the IL-6 subfamily have been shown to be potentially important cytokines in the pathogenesis of rheumatoid arthritis (Carroll *et al*, 1998). Favourable effects on disease activity have been observed in rheumatoid arthritis patients treated with a monoclonal anti-IL-6 antibody (Wendling *et al*, 1993). It remains to be seen whether greater benefits can be obtained if other members of the subfamily or multiple members are antagonised (Carroll *et al*, 1998).

Sant-7 is an IL-6 receptor antagonist, under development by Sigma-Tau for the systemic treatment of multiple myeloma, topical treatment of Kaposi's sarcoma and *ex-vivo* treatment of myeloma. It is also considered to have potential in B-cell lymphomas, rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus and psoriasis (*Scrip* 2290, 25 November 1997 p9).

5.6.2 T-614

T-614 is an oral anti-inflammatory agent, under development by Toyama. It suppresses the production of IL-1, IL-6, IL-8 and TNF (Eisai press release, October 1998). It is licensed to Eisai for co-development and co-marketing in Japan. Eisai will help complete Phase III trials before a joint-approval application is filed (*Scrip* 2382, 28 October 1998 p10).

It is in Phase III clinical trials in Japan as an antirheumatic agent and is in preparation for Phase IIa trials in the UK (trials were due in late 1998). In clinical trials, results so far suggest that T-614 significantly decreases the inflammatory response as measured by ESR, the production of C-reactive protein and immunoglobulins. In rheumatoid arthritis it showed a rapid and high level of efficacy with a good safety profile (*Scrip* 2140, 25 June 1996 p24; Eisai press release, October 1998).

This product, which Toyama says has a better efficacy and side effect profile than existing treatments, has a rapid onset of action and is expected to be effective in patients unresponsive to other therapies.

5.6.3 Interleukin-10

A cytokine that has been studied in rheumatoid arthritis and is currently under investigation in psoriatic arthritis is IL-10 (Maini *et al*, 1997). This cytokine is thought to inhibit the production of IL-1 and TNF-α from macrophages, suggesting that it has potential in the treatment of immune-mediated diseases dominated by Th1 (IFN-γ producing) T-cells (Katsikis *et al*, 1994). Interleukin-10 has been shown to have anti-inflammatory and immunoregulatory properties (see Keystone *et al*, 1998 for detailed information). A key characteristic is its ability to inhibit the generation of proinflammatory cytokines and chemokines by monocytes, polymorpholeukocytes and eosinophils. It has been shown to inhibit IL-1, IL-12, IL-6, TNF, GM-CSF and G-CSF and the chemokines IL-8 and macrophage inhibitory protein-1B (MIP-1B) (Keystone *et al*, 1998). It also blocks T-cell responses to specific antigens. Consequently, considerable research is in progress to determine a possible role for IL-10 as a therapeutic agent for the treatment of rheumatoid arthritis.

DNAX (Schering-Plough) has cloned and expressed human IL-10. Phase I and II clinical trials for rheumatoid arthritis are in progress (see Keystone *et al*, 1998 for references) and trends towards improved rheumatoid arthritis disease activity have been demonstrated.

5.7 TCR Peptides

TCR peptides elicit an immune response in regulatory T-cells which release cytokines that selectively suppress the activity of pathogenic T-lymphocytes in certain autoimmune diseases. Connetics Corporation is using the technology to develop products to treat chronic connective tissue and autoimmune diseases such as rheumatoid arthritis, psoriasis and IBD. Each autoimmune disease is thought to be characterised by utilisation of a particular Vβ region on T-lymphocytes. If the Vβ regions relevant to a particular disease can be identified, TCR vaccines specific for different diseases could be produced.

Results of a Phase II trial with Immune Response Corporation's therapeutic vaccine for rheumatoid arthritis, IR501, have been published by Moreland *et al* (1998). The study was undertaken to determine the safety and efficacy of the product, a therapeutic vaccine which is

composed of a combination of three TCR-derived peptides (Vβ 3, Vβ 14 and Vβ 17) in Incomplete Freund's Adjuvant (IFA), in patients with rheumatoid arthritis.

It was a double-blind, placebo-controlled, multicentre trial in a total of 99 patients with active rheumatoid arthritis. The vaccine (or placebo) was administered as a single intramuscular injection at weeks 0, 4, 8 and 20. IR501 was safe and well tolerated. Efficacy was measured according to the ACR 20% improvement criteria and showed a significant improvement in patients treated with IR501. Additional clinical trials are planned.

5.8 ICE inhibitors

The ICE and its homologues are potential therapeutic intervention targets for the treatment of inflammatory diseases (Dinarello & Wolff, 1993; Livingston, 1996). ICE is a cysteine protease responsible for the proteolytic activation of IL-1β precursor to the biologically active form, IL-1β. IL-1β is a principal mediator of inflammation in rheumatoid arthritis (Lebsack *et al,* 1993) and is the major osteoclast activating factor in osteoarthritis (van de Loo *et al,* 1995).

Inhibition of ICE is being explored to design both reversible inhibitors and irreversible inactivators of the enzyme. Such compounds are able to block the release of IL-1β from monocytes.

The US company, Vertex, has begun the first clinical trial with an oral small molecule inhibitor of ICE (caspase 1). The compound, HMR 3480/VX-740, is being developed with Hoechst Marion Roussel as a treatment for rheumatoid arthritis. ICE regulates the production of IL-1 and IFN-γ (*Scrip* 2411, 12 February 1999 p13).

BASF Pharma has established a partnership with Warner-Lambert on ICE inhibitors for rheumatoid arthritis and stroke.

5.9 IMPDH inhibitors

IMPDH is an enzyme that enables lymphocyte proliferation and recruitment by catalysing a key step in one of two DNA nucleotide biosynthesis pathways. Inhibition of IMPDH appears to selectively suppress immune system cells while leaving other cells unaffected. This may play an important role in down-regulating inappropriate immune responses as seen in rheumatoid arthritis and other inflammatory diseases.

VX-497 is an IMPDH inhibitor, under development by Vertex for the treatment of hepatitis C, asthma, psoriasis, rheumatoid arthritis, systemic lupus erythematosus and organ transplant rejection (*Scrip* 2374, 30 September 1998 p24). The 3D atomic structure of IMPDH has been solved and the company has developed novel, orally-bioavailable inhibitors of the enzyme.

It is in Phase II trials for hepatitis C and psoriasis. Phase I trials in autoimmune diseases in the UK have been completed and preparations for Phase II are underway (*Scrip* 2331, 1 May 1998 p15).

Only one specific inhibitor of IMPDH is currently on the market in the US. This is Roche's mycophenolate mofetil (CellCept) which is approved for acute kidney transplant and heart transplant rejection. It is in Phase III trials for rheumatoid arthritis (see Section 5.4).

5.10 Therapeutic vaccines

M&E Biotech, is developing therapeutic vaccines for chronic diseases with an unmet medical need using its novel platform technology, AutoVac (*Scrip* 2386, 11 November 1998 p27).

Many diseases are associated with the over-expression of normal proteins, such as TNF-α in inflammatory diseases. The AutoVac technology involves inserting an antigenic fragment into these pathogenic proteins. This leads to the immune system recognising the pathogenic self-proteins as foreign and producing antibodies against them. Rapid and strong cross-reactive immune responses have been demonstrated. The company is developing an anti-TNF-α vaccine against rheumatoid arthritis, Crohn's disease and cancer cachexia. The product, which is exclusively licensed to Ferring for all human diseases, is expected to enter clinical trials for these indications in the first half of 1999.

5.11 Adhesion molecule inhibitors

The ability of cells to adhere to each other and to other components of the extracellular matrix, is fundamental to all multicellular organisms. Cell recognition and adhesion are essential for normal development and for maintenance of tissue integrity, tissue repair and immune functions such as antigen recognition, cell mediated cytotoxicity and lymphocyte recirculation. These events are mediated by adhesion molecules. In recent years the role of adhesion molecules in rheumatic disease has become the focus of attention and studies on these molecules have prompted the search for anti-inflammatory agents that interfere with adhesion-mediated events in the inflammatory process.

A significant aspect of inflammatory disease is the recruitment of leukocytes from the circulation and their interaction with other cell types (macrophages, dendritic cells, fibroblasts) within the inflamed tissue. The adhesion molecules involved in this process are selectins, integrins, the immunoglobulin supergene family (includes ICAM) and the CD44 family.

Adhesion molecules are an attractive target for inhibiting leukocyte trafficking and T-cell activation. However, a potential problem for their use as anti-inflammatory targets is their ubiquitous nature. This makes it difficult to develop drugs without unwanted side effects. Nevertheless, some companies are responding to the challenge. Under development are inhibitors to the selectins, ELAM-1, VCAM-1 and ICAM-1.

Further reading regarding adhesion molecules and rheumatic diseases can be found at the Arthritis Research Campaign website (www.arc.org.uk/trs34.htm) and in a review by Cronstein and Weissmann (1993).

5.12 Gene therapy

The rheumatoid joint has a great advantage with respect to the practicality of gene therapy. It is an enclosed space into which genes can be targeted by direct injection. The goal would be to introduce genes that promote the production of beneficial anti-inflammatory molecules such as IL-4, IL-10, IL-1r or compounds which block TNF.

The underlying concept of gene therapy is that normal genes can be transferred into the cells of an affected host in such a way that they express their functional gene product, correct the molecular deficiency and either cure or improve the condition of the disease. Rheumatoid

arthritis is not due to a single gene mutation but, nevertheless, research has identified pathways in the pathogenesis of the disease which would be suitable for correction through gene transfer.

The first clinical trial for rheumatoid arthritis, which investigated the feasibility, safety and efficacy of transferring a potentially anti-arthritic cytokine gene into human joints affected by rheumatoid arthritis was reported by Evans *et al* (1996). Currently two additional clinical trials are in progress (comment in Jorgensen & Gay, 1998).

Researchers at the University of Pittsburg have tested a gene therapy for arthritis and obtained promising results in animal models of the disease (Ghivizzani *et al*, 1998). Gene therapy, injected into one diseased joint, unexpectedly produced systemic effects and led to improvement in other diseased joints of treated animals. The best therapeutic effects were obtained with a combination of genes for the IL-1 and TNF-α receptors, delivered in an adenovirus vector. Knee joints injected with this combination showed an 85–90% reduction in white blood cell levels, and a similar protection of cartilage.

The same group is also studying the safety of gene therapy for arthritis in a clinical protocol, involving nine postmenopausal women, which began in July 1996. Here, a gene coding for IL-1ra is administered in a retrovirus vector to fibroblasts that have been extracted from patients' joints. These gene-carrying fibroblasts are then returned to the patient's arthritic knuckle joint for a week, after which the treated knuckle is removed and replaced with an artificial joint. The removed tissue is examined for evidence of gene therapy activity. To date, all the patients tested have shown evidence of gene expression and have had no adverse effects (*Scrip* 2335, 15 May 1998 p27).

Osiris Therapeutics has launched StemScreen, a functional genomics programme for diseases affecting the body's structural and connective tissues. According to the Baltimore-based company, it is the first gene and drug discovery technology based on normal human mesenchymal stem cells, the progenitor cells responsible for the formation of these tissues. The company predicts that the system, which has assays to identify molecules that regulate mesengenesis (tissue formation) and determine their function in normal tissue, will assist in the discovery of new drugs for obesity, arthritis, immune disorders, infertility and osteoporosis (*Scrip* 2335, 15 May 1998 p18).

Chiroscience has identified a novel gene which acts as an 'on/off' switch for the immune system (*Scrip* 2375, 2 October 1998 p5). The company believes the immune system gene, and its associated gene product, control a hitherto unknown signalling pathway which will provide a host of potential drug discovery targets for autoimmune and inflammatory diseases, as well as a new approach to treating cancer and acquired immunodeficiency syndrome (AIDS). It has cloned and filed patents on the gene and is now studying the action of its product, which it says, regulates the activity of CD4 T-cells.

The gene is the human homologue of the mouse gene which, when defective, causes the 'Scurfy' mutation. The Scurfy mouse, which was first described in 1949, cannot down-regulate its immune system and suffers a massive autoimmune reaction which leads to death after about 3 weeks. According to Chiroscience, the product of the normal gene is essential for the control of the normal immune response, while a non-functioning gene leads to an enhanced immune response. The company considers that the finding validates the use of mouse genetics, which allows the study of disease states which do not occur or have not been

observed in humans and is now looking for evidence that the massive autoimmune reaction seen in Scurfy mice occurs in humans.

Chiroscience believes the gene discovery offers two therapeutic opportunities:

- Immune stimulation, by inhibition of the gene product. This could be of use in cancer and human immunodeficiency virus (HIV)
- Immune regulation by intervention in the signalling pathway to switch off an abnormal immune response. This could be tapped for use in diseases such as rheumatoid arthritis, diabetes, psoriasis, Crohn's disease, ulcerative colitis and allergy

Hyseq has identified a new IL-1 gene, IL-1Hy273, and its associated protein, which may have therapeutic uses in the treatment of inflammatory diseases. Two previously identified IL-1s, IL-1α and IL-1β, stimulate the inflammatory process, while a third, IL-1ra, inhibits inflammation. The new gene, is being initially investigated for rheumatoid arthritis and IBD (*Scrip* 2364, 26 August 1998 p17).

Zeneca is conducting an analysis of the DNA from people with rheumatoid arthritis to find genes which increase their susceptibility to the disease.

5.13 Thalidomide

Celgene has launched the controversial drug thalidomide (Thalomid) in the US for treatment of moderate to severe erythema nodosum leprosum, a severe and debilitating condition associated with leprosy. Distribution of thalidomide has been severely restricted because of concerns about its well-known potential for causing birth defects (*Scrip* 2354, 22 July 1998 p19). However, it is also being investigated in a number of other indications including rheumatoid arthritis.

While the precise mechanism of action of the drug is unknown, available data from *in vitro* studies suggest that the immunologic effects may be related to suppression of excessive production of TNF-α. In addition, the compound may decrease the molecular adhesion to immune cells.

5.14 Mononuclear cell therapy

Viragen has acquired rights to Inflammatics' lead product, LeukoVAX, an immunomodulating mononuclear cell preparation, which is in Phase I/II trials for the treatment of rheumatoid arthritis. According to Viragen, an open-label pilot study of LeukoVAX for rheumatoid arthritis showed that a majority of patients experienced an improvement in efficacy markers. The current Phase I/II trials of LeukoVAX, which is administered once every 5 weeks, are expected to be completed in 1999. Inflammatics hopes that LeukoVAX will demonstrate a disease-modifying effect and believes it also has potential in other cell-mediated autoimmune diseases (*Scrip* 2371, 18 September 1998 p14).

5.15 Cathepsins

AxyS has discovered the 3D structure of cathepsin S, a protease associated with normal degradation of cellular protein and linked with several inflammatory diseases, including arthritis, asthma and other autoimmune diseases (McGrath *et al*, 1998). Detailed knowledge

of the protease's 3D structure should allow the design of potent and selective inhibitors of the enzyme. AxyS has already identified a number of sub-nanomolar, reversible selective inhibitors of the molecule as part of an ongoing programme covering several members of the papain group of cysteine proteases (*Scrip* 2356, 29 July 1998 p13).

5.16 Prednisolone

A meta-analysis of 10 studies on the use of prednisolone in rheumatoid arthritis found that the corticosteroid was superior to placebo and NSAIDs in terms of effects on joint tenderness and pain. The study, reported by Gotzsche and Johansen (1998), also found that the risk of adverse effects with the corticosteroid was acceptable. However, an editorial in the same issue (Dennison & Cooper, 1998), disagreed with the authors' conclusion that intermittent courses of prednisolone at doses of up to 15mg daily should be more widely used. It points out that stepping down steroid treatment is difficult, and so patients are often exposed to the risk of long-term adverse effects (*Scrip* 2320, 25 March 1998 p27).

A product consisting of prednisolone linked at C-21 with farnesil acid is in development. It penetrates the epidermis to reach the inflamed area and has few systemic side effects at therapeutic doses.

5.17 Gene regulators

Ares-Serono and Signal Pharmaceuticals have entered into a multi-year collaboration to identify small-molecule modulators of the NFκB gene regulation pathway. NFκB is a key regulator of a broad set of inflammatory genes implicated in diseases such as rheumatoid arthritis, MS, asthma and psoriasis. The research will initially focus on two proteins that regulate the activation of NFκB, namely IKK-1 and IKK-2, as well as a third regulatory protein recently identified by Signal and its academic collaborators (*Scrip* 2291, 9 December 1997 p7).

Another category of gene-regulating drugs which might be used as immunosuppressive agents includes the lymphocyte-specific nucleoside analogues, a class of drugs which has been shown to have activity against DNA synthesis and repair by interfering with DNA polymerases and ribonucleotide reductase. One such agent is the adenosine analogue, fludarbine, which is being studied in patients with rheumatoid arthritis (Davis *et al*, 1998). Lymphocytes have a high ratio of deoxycytidine kinase to 5'-nucleotidase which favours the formation of toxic phosphate derivatives of these compounds and explains their selectivity towards lymphocytes. They target both resting and proliferating lymphocytes. In resting lymphocytes they activate the endogenous nucleases and promote apoptosis and in proliferating lymphocytes they inhibit DNA synthesis (Davis *et al*, 1998).

5.18 MAP kinase inhibitors

The MAP kinases are a family of structurally-related enzymes involved in intracellular signalling pathways that enable cells to respond to their environment. Blocking MAP kinases is a potential way of inhibiting cytokine translation.

Vertex's MAP kinase research programme focuses on the p38 MAP kinase, an enzyme involved in the onset and progression of inflammation and programmed cell death. When activated, p38 MAP kinase triggers the production of the cytokines IL-1 and TNF-α. Vertex and Kissei are collaborating on the design, development and commercialisation of inhibitors

of p38 MAP kinase in order to develop novel orally-active drugs to treat inflammatory and neurological diseases.

5.19 Matrix MMPs

Matrix MMPs are a structurally-related family of endoproteinases of which at least 15 have been identified in humans. The prefix metallo- refers to the fact that they all contain a zinc atom at their active site. At physiological pH these enzymes can degrade most of the components of the extracellular matrix and under normal conditions, they play a role in wound healing and other processes involving tissue remodelling.

The activity of MMPs is tightly regulated by gene expression and by the fact that they are secreted in a pro-enzyme form which requires removal of an amino-terminal domain for the expression of enzyme activity. Once activated, they are usually regulated by either non-specific protease inhibitors or by tissue-specific inhibitors of MMPs (TIMPs). Thus, under normal physiological conditions the activity of MMPs is tightly controlled. Uncontrolled over-production of MMPs is involved in the pathology of many diseases including arthritis and IBD.

A number of companies are developing matrix MMP inhibitors for the treatment of arthritis (see Tables 5.1 and 5.2).

5.20 Glucose-6 phosphate dehydrogenase inhibitors

CBF-BS2 is being developed by KS Biomedix for the treatment of rheumatoid arthritis. It acts by reversing the abnormal increases in glucose-6 phosphate dehydrogenase seen in the synovial lining cells of rheumatoid arthritis sufferers. A Phase II trial of an oral formulation has been carried out in 19 patients with rheumatoid arthritis with a total of 292 affected joints. Patients were assessed after 4 weeks for the reduction in the number of swollen joints. The study showed that the total number of swollen joints in the treatment group decreased from 235 to 147 (a 37% improvement). This compares to 2% in the placebo group. These preliminary results set the scene for a 120-patient randomised double-blind Phase II trial using a new formulation with improved stability. The company believe that a controlled-release formulation will probably need to be developed.

5.21 Phosphodiesterase IV inhibitors

Enhancement of intracellular cyclic adenosine monophosphate (cAMP) levels has anti-inflammatory effects which are known to be mediated by the modulation of signal transduction pathways in which cyclic AMP is a second messenger. A key enzyme in the regulation of cAMP levels is phosphodiesterase (PDE), which inactivates cAMP by catalysing the hydrolysis of the 3'-phosphodiester bond, to form 5'-AMP. Non-selective PDE inhibitors have an unfavourable side effect profile which would be unacceptable. Interest in cyclic nucleotide PDEs was renewed by the recognition of multiple, distinct PDE isozymes, differences in cellular distribution between isozymes and the synthesis of inhibitors with selectivity for specific isozymes. These observations suggest that there are opportunities for the development of compounds targeted to a particular isoform, predominating in a selected target tissue. However, one disadvantage is that there are marked species differences between PDE isoenzymes which makes the therapeutic action of compounds difficult to predict from animal models.

Eight families of PDE isozymes exist, each containing multiple isoforms. PDE IV, which has four subtypes, A, B, C and D is the predominant cAMP-specific PDE in inflammatory cells and the main target of anti-inflammatory research. Several compounds are in development with potential as anti-arthritis therapies (see Tables 5.1 and 5.2).

5.22 Capsaicin cream

Zacin, an 0.025% capsaicin cream for pain relief in osteoarthritis, has been launched by Bioglan in the UK. Further launches in Europe are planned (*Scrip* 2335, 15 May 1998 p25).

The ACR recommends topical capsaicin as a first-line therapy for patients with symptomatic osteoarthritis of the knee. The cream is recommended after non-pharmacologic modalities (weight loss, exercise) and paracetamol but before the use of alternative analgesics such as low-dose ibuprofen and other NSAIDs.

Capsaicin, originally obtained from chilli peppers, relieves pain by depleting substance P, the primary neurotransmitter involved in the transmission of pain. In osteoarthritis, the cream is applied to the affected joint several times a day, and acts to deplete substance P from the afferent sensory neurones that carry the pain message to the brain. As this depletion is a gradual process, the pain relief obtained is progressive, with maximum benefit obtained after a few weeks of treatment.

In one clinical trial, continued for 12 weeks, all of 70 patients with osteoarthritis reported that their pain had decreased by about one-third. In a separate arm of this study, there was also some evidence for a beneficial effect in rheumatoid arthritis. Bioglan may apply for this indication in the future.

Capsaicin cream does not appear to be systemically absorbed, and the only side effect is a stinging or burning sensation at the site of application but this decreases over time. Zacin has an UK National Health Service cost of £15.04 ($24.7) for a 48g tube (sufficient for a month's treatment of one joint).